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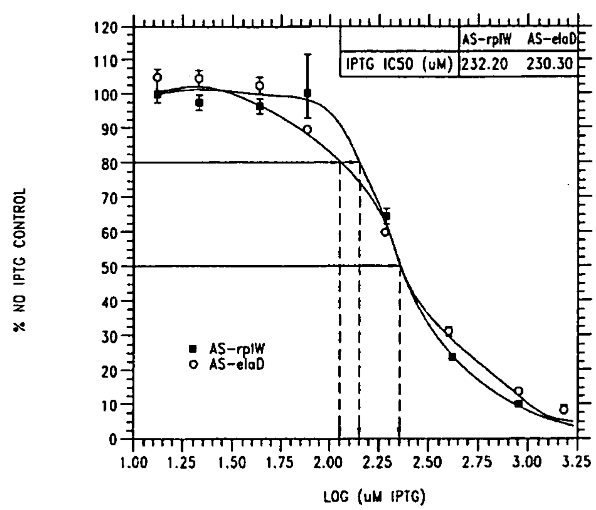
(54) Title: IDENTIFICATION OF ESSENTIAL GENES IN MICROORGANISMS



(57) Abstract: The sequences of antisense nucleic acids which inhibit the proliferation of prokaryotes are disclosed. Cell based assays which employ the antisense nucleic acids to identify and develop antibiotics are also disclosed. The antisense nucleic acids can also be used to identify proteins required for proliferation, express these proteins or portions thereof, obtain antibodies capable of specifically binding to the expressed proteins, and to use those expressed proteins as a screen to isolate candidate molecules for rational drug discovery programs. The nucleic acids can also be used to screen for homologous nucleic acids that are required for proliferation in cells other than Staphylococcus aureus, Salmonella typhimurium, Klebsiella pneumoniae, and Pseudomonas aeruginosa. The nucleic acids of the present invention can also be used in various assay systems to screen for proliferation required genes in other organisms.

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IDENTIFICATION OF ESSENTIAL GENES IN MICROORGANISMS

Sequence Listing

The present application is being filed along with quadruplicate copies of a CD-ROM marked "Copy 1 - SEQUENCE LISTING PART," "Copy 2 - SEQUENCE LISTING PART," "Copy 3 - SEQUENCE LISTING PART," and "CRF" containing a Sequence Listing in electronic format. The quadruplicate copies of the CD-ROM each contain a file entitled 034VPC_final.ST25.txt, created on March 15, 2002, which is 181,323,311 bytes in size.

Background of the Invention

Since the discovery of penicillin, the use of antibiotics to treat the ravages of bacterial infections has saved millions of lives. With the advent of these "miracle drugs," for a time it was popularly believed that humanity might, once and for all, be saved from the scourge of bacterial infections. In fact, during the 1980s and early 1990s, many large pharmaceutical companies cut back or eliminated antibiotics research and development. They believed that infectious disease caused by bacteria finally had been conquered and that markets for new drugs were limited. Unfortunately, this belief was overly optimistic.

The tide is beginning to turn in favor of the bacteria as reports of drug resistant bacteria become more frequent. The United States Centers for Disease Control announced that one of the most powerful known antibiotics, vancomycin, was unable to treat an infection of the common *Staphylococcus aureus* (staph). This organism is commonly found in our environment and is responsible for many nosocomial infections. The import of this announcement becomes clear when one considers that vancomycin was used for years to treat infections caused by *Staphylococcus* species as well as other stubborn strains of bacteria. In short, bacteria are becoming resistant to our most powerful antibiotics. If this trend continues, it is conceivable that we will return to a time when what are presently considered minor bacterial infections are fatal diseases.

Over-prescription and improper prescription habits by some physicians have caused an indiscriminate increase in the availability of antibiotics to the public. The patients are also partly responsible, since they will often improperly use the drug, thereby generating yet another population of bacteria that is resistant, in whole or in part, to traditional antibiotics.

The bacterial pathogens that have haunted humanity remain, in spite of the development of modern scientific practices to deal with the diseases that they cause. Drug resistant bacteria are now an increasing threat to the health of humanity. A new generation of antibiotics is needed to once again deal with the pending health threat that bacteria present.

Discovery of New Antibiotics

As more and more bacterial strains become resistant to the panel of available antibiotics, new antibiotics are required to treat infections. In the past, practitioners of pharmacology would have to rely upon traditional methods of drug discovery to generate novel, safe and efficacious compounds for the treatment of disease. Traditional drug discovery methods involve blindly testing potential drug candidate-molecules, often selected at random, in the hope that one might prove to be

an effective treatment for some disease. The process is painstaking and laborious, with no guarantee of success. Today, the average cost to discover and develop a new drug exceeds US $500 million, an```d the average time from laboratory to patient is 15 years. Improving this process, even incrementally, would represent a huge advance in the generation of novel antimicrobial agents.

Newly emerging practices in drug discovery utilize a number of biochemical techniques to provide for directed approaches to creating new drugs, rather than discovering them at random. For example, gene sequences and proteins encoded thereby that are required for the proliferation of a cell or microorganism make excellent targets since exposure of bacteria to compounds active against these targets would result in the inactivation of the cell or microorganism. Once a target is identified, biochemical analysis of that target can be used to discover or to design molecules that interact with and alter the functions of the target. Use of physical and computational techniques to analyze structural and biochemical properties of targets in order to derive compounds that interact with such targets is called rational drug design and offers great potential. Thus, emerging drug discovery practices use molecular modeling techniques, combinatorial chemistry approaches, and other means to produce and screen and/or design large numbers of candidate compounds.

Nevertheless, while this approach to drug discovery is clearly the way of the future, problems remain. For example, the initial step of identifying molecular targets for investigation can be an extremely time consuming task. It may also be difficult to design molecules that interact with the target by using computer modeling techniques. Furthermore, in cases where the function of the target is not known or is poorly understood, it may be difficult to design assays to detect molecules that interact with and alter the functions of the target. To improve the rate of novel drug discovery and development, methods of identifying important molecular targets in pathogenic cells or microorganisms and methods for identifying molecules that interact with and alter the functions of such molecular targets are urgently required.

Escherichia coli represents an excellent model system to understand bacterial biochemistry and physiology. The estimated 4288 genes scattered along the 4.6×10^6 base pairs of the *Escherichia coli* (*E. coli*) chromosome offer tremendous promise for the understanding of bacterial biochemical processes. In turn, this knowledge will assist in the development of new tools for the diagnosis and treatment of bacteria-caused human disease. The entire *E. coli* genome has been sequenced, and this body of information holds a tremendous potential for application to the discovery and development of new antibiotic compounds. Yet, in spite of this accomplishment, the general functions or roles of many of these genes are still unknown. For example, the total number of proliferation-required genes contained within the E. coli genome is unknown, but has been variously estimated at around 200 to 700 (Armstrong, K.A. and Fan, D.P. Essential Genes in the *metB-malB* Region of *Escherichia coli* K12, 1975, J. Bacteriol. 126: 48-55).

Staphylococcus aureus is a Gram positive microorganism which is the causative agent of many infectious diseases. Local infection by *Staphylococcus aureus* can cause abscesses on skin and cellulitis in subcutaneous tissues and can lead to toxin-related diseases such as toxic shock and

scalded skin syndromes. *Staphylococcus aureus* can cause serious systemic infections such as osteomyelitis, endocarditis, pneumonia, and septicemia. *Staphylococcus aureus* is also a common cause of food poisoning, often arising from contact between prepared food and infected food industry workers. Antibiotic resistant strains of *Staphylococcus aureus* have recently been identified, including those that are now resistant to all available antibiotics, thereby severely limiting the options of care available to physicians.

Pseudomonas aeruginosa is an important Gram negative opportunistic pathogen. It is the most common Gram negative found in nosocomial infections. *P. aeruginosa* is responsible for 16% of nosocomial pneumonia cases, 12% of hospital-acquired urinary tract infections, 8% of surgical wound infections, and 10% of bloodstream infections. Immunocompromised patients, such as neutropenic cancer and bone marrow transplant patients, are particular susceptible to opportunistic infections. In this group of patients, *P. aeruginosa* is responsible for pneumonia and septicemia with attributable deaths reaching 30%. *P. aeruginosa* is also one of the most common and lethal pathogens responsible for ventilator-associated pneumonia in intubated patients, with directly attributable death rates reaching 38%. Although *P. aeruginosa* outbreaks in burn patients are rare, it is associated with 60% death rates. In the AIDS population, *P. aeruginosa* is associated with 50% of deaths. Cystic fibrosis patients are characteristically susceptible to chronic infection by *P. aeruginosa*, which is responsible for high rates of illness and death. Current antibiotics work poorly for CF infections (Van Delden & Igelwski. 1998. Emerging Infectious Diseases 4:551-560; references therein).

The gram negative enteric bacterial genus, *Salmonella*, encompasses at least 2 species. One of these, *S. enterica*, is divided into multiple subspecies and thousands of serotypes or serovars (Brenner, et al. 2000 J. Clin. Microbiol. 38:2465-2467). The *S. enterica* human pathogens include serovars Typhi, Paratyphi, Typhimurium, Cholerasuis, and many others deemed so closely related that they are variants of a widespread species. Worldwide, disease in humans caused by *Salmonella* is a very serious problem. In many developing countries, *S. enterica* ser. Typhi still causes often-fatal typhoid fever. This problem has been reduced or eliminated in wealthy industrial states. However, enteritis induced by Salmonella is widespread and is the second most common disease caused by contaminated food in the United States (Edwards, BH 1999 "Salmonella and Shigella species" Clin. Lab Med. 19(3):469-487). Though usually self-limiting in healthy individuals, others such as children, seniors, and those with compromising illnesses can be at much greater risk of serious illness and death.

Some *S. enterica* serovars (e.g. Typhimurium) cause a localized infection in the gastrointestinal tract. Other serovars (i.e. Typhi and Paratyphi) cause a much more serious systemic infection. In animal models, these roles can be reversed which has allowed the use of the relatively safe *S. enterica* ser. Typhimurium as a surrogate in mice for the typhoid fever agent, *S. enterica* ser. Typhi. In mice, *S. enterica* ser Typhimurium causes a systemic infection similar in outcome to typhoid fever. Years of study of the *Salmonella* have led to the identification of many determinants

of virulence in animals and humans. *Salmonella* is interesting in its ability to localize to and invade the intestinal epithelium, induce morphologic changes in target cells via injection of certain cell-remodeling proteins, and to reside intracellularly in membrane-bound vesicles (Wallis, TS and Galyov, EE 2000 "Molecular basis of *Salmonella*-induced enteritis." Molec. Microb. 36:997-1005; Falkow, S "The evolution of pathogenicity in Escherichia, Shigella, and Salmonella," Chap. 149 in Neidhardt, et al. eds pp 2723-2729; Gulig, PA "Pathogenesis of Systemic Disease," Chap. 152 in Neidhardt, et al. ppp 2774-2787). The immediate infection often results in a severe watery diarrhea but *Salmonella* also can establish and maintain a subclinical carrier state in some individuals. Spread is via food contaminated with sewage.

The gene products implicated in *Salmonella* pathogenesis include type three secretion systems (TTSS), proteins affecting cytoplasmic structure of the target cells, many proteins carrying out functions necessary for survival and proliferation of *Salmonella* in the host, as well as "traditional" factors such as endotoxin and secreted exotoxins. Additionally, there must be factors mediating species-specific illnesses. Despite this most of the genomes of *S. enterica* ser. Typhi (see http://www.sanger.ac.uk/Projects/S_typhi/ for the genome database) and *S. enterica* ser. Typhimurium (see http://genome.wustl.edu/gsc/bacterial/salmonella.shtml for the genome database) are highly conserved and are mutually useful for gene identification in multiple serovars. The Salmonella are a complex group of enteric bacteria causing disease similar to but distinct from other gram negative enterics such as *E. coli* and have been a focus of biomedical research for the last century.

Enterococcus faecalis, a Gram positive bacterium, is by far the most common member of the enterococci to cause infections in humans. *Enterococcus faecium* generally accounts for less than 20% of clinical isolates. Enterococci infections are mostly hospital-acquired though they are also associated with some community-acquired infections. Of nosocomial infections enterococci account for 12% of bacteremia, 15% of surgical wound infections, 14% of urinary tract infections, and 5 to15% of endocarditis cases (Huycke, M. M., D. F., Sahm and M. S. Gilmore. 1998. Emerging Infectious Diseases 4:239-249). Additionally enterococci are frequently associated with intraabdominal and pelvic infections. Enterococci infections are often hard to treat because they are resistant to a vast array of antimicrobial drugs, including aminoglycosides, penicillin, ampicillin and vancomycin. The development of multiple-drug resistant (MDR) enterococci has made this bacteria a major concern for treating nosocomial infections.

Current drug discovery methods involve screening large number of prospective therapeutic compounds to identify those that are effective therapeutic agents or that can be optimized to provide an effective therapeutic agents. For example, the compounds to be evaluated for therapeutic activity may be members of a library of compounds generated by combinatorial chemistry or members of a library of natural products.

Unfortunately, current methods are laborious and time consuming and may yield compounds which have already been identified or which act on gene products which are already

targeted by an existing therapeutic agent. In addition, a large number of compounds have been identified which have antimicrobial activity but which cannot be administered to individuals suffering from infection due to the fact that their targets are unknown.

The above reasons underscore the urgency of developing new antibiotics that are effective against *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa,* and *Salmonella typhimurium*. Accordingly, there is an urgent need for more novel methods to identify and characterize bacterial genomic sequences that encode gene products involved in proliferation, and are thereby potential new targets for antibiotic development. Likewise, there is a need for rapid screening techniques which yield novel compounds or compounds which act on novel targets as well as a need for methods which permit the identification of the target on which a compound with antimicrobial activity acts.

Prior to the present invention, the discovery of *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa,* and *Salmonella typhimurium* genes required for proliferation of the microorganism was a painstaking and slow process. Rapid screening techniques for identifying novel targets on which novel compounds act were undeveloped. While the detection and identification of new cellular drug targets within a *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa,* and *Salmonella typhimurium* cell is key for novel antibiotic development and effective treatment, the current methods of drug target discovery available prior to this invention have required painstaking processes requiring years of effort.

Summary of the Invention

Some aspects of the present invention are described in the numbered paragraphs below.

1. A purified or isolated nucleic acid sequence comprising a nucleotide sequence consisting essentially of one of SEQ ID NOs: 1-6213, wherein expression of said nucleic acid inhibits proliferation of a cell.

2. The nucleic acid sequence of Paragraph 1, wherein said nucleotide sequence is complementary to at least a portion of a coding sequence of a gene whose expression is required for proliferation of a cell.

3. The nucleic acid of Paragraph 1, wherein said nucleic acid sequence is complementary to at least a portion of a nucleotide sequence of an RNA required for proliferation of a cell.

4. The nucleic acid of Paragraph 3, wherein said RNA is an RNA comprising a sequence of nucleotides encoding more than one gene product.

5. A purified or isolated nucleic acid comprising a fragment of one of SEQ ID NOs.: 1-6213, said fragment selected from the group consisting of fragments comprising at least 10, at least 20, at least 25, at least 30, at least 50 and more than 50 consecutive nucleotides of one of SEQ ID NOs: 1-6213.

6. The fragment of Paragraph 5, wherein said fragment is included in a nucleic acid obtained from an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

7. The fragment of Paragraph 5, wherein said fragment is included in a nucleic acid obtained from an organism other than *Escherichia coli.*

8. A vector comprising a promoter operably linked to the nucleic acid of any one of Paragraphs 1-7.

9. The vector of Paragraph 8, wherein said promoter is active in a microorganism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis,*

Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis and any species falling within the genera of any of the above species.

10. A host cell containing the vector of Paragraph 8 or Paragraph 9.

11. A purified or isolated antisense nucleic acid comprising a nucleotide sequence complementary to at least a portion of an intragenic sequence, intergenic sequence, sequences spanning at least a portion of two or more genes, 5' noncoding region, or 3' noncoding region within an operon comprising a proliferation-required gene whose activity or expression is inhibited by an antisense nucleic acid comprising the nucleotide sequence of one of SEQ ID NOs.: 1-6213.

12. The purified or isolated antisense nucleic acid of Paragraph 11, wherein said antisense nucleic acid is complementary to a nucleic acid from an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma*

urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis and any species falling within the genera of any of the above species.

13. The purified or isolated antisense nucleic acid of Paragraph 11, wherein said nucleotide sequence is complementary to a nucleotide sequence of a nucleic acid from an organism other than *E. coli*.

14. The purified or isolated antisense nucleic acid of Paragraph 11, wherein said proliferation-required gene comprises a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397.

15. A purified or isolated nucleic acid comprising a nucleotide sequence having at least 70% identity to a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, fragments comprising at least 25 consecutive nucleotides of SEQ ID NOs.: 1-6213, the nucleotide sequences complementary to SEQ ID NOs.: 1-6213 and the sequences complementary to fragments comprising at least 25 consecutive nucleotides of SEQ ID NOs.: 1-6213 as determined using BLASTN version 2.0 with the default parameters.

16. The purified or isolated nucleic acid of Paragraph 15, wherein said nucleic acid is obtained from an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

17. The nucleic acid of Paragraph 15, wherein said nucleic acid is obtained from an organism other than *E. coli*.

18. A vector comprising a promoter operably linked to a nucleic acid encoding a polypeptide whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence of any one of SEQ ID NOs.: 1-6213.

19. The vector of Paragraph 18, wherein said nucleic acid encoding said polypeptide is obtained from an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

20. The vector of Paragraph 18, wherein said nucleotide sequence encoding said polypeptide is obtained from an organism other than *E. coli*.

21. A host cell containing the vector of Paragraph 18.

22. The vector of Paragraph 18, wherein said polypeptide comprises a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 42398-78581.

23. The vector of Paragraph 18, wherein said promoter is operably linked to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397.

24. A purified or isolated polypeptide comprising a polypeptide whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence of any one of SEQ ID NOs.: 1-6213, or a fragment selected from the group consisting of fragments comprising at least 5,

at least 10, at least 20, at least 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of one of the said polypeptides.

25. The polypeptide of Paragraph 24, wherein said polypeptide comprises an amino acid sequence of any one of SEQ ID NOs.: 42398-78581 or a fragment comprising at least 5, at least 10, at least 20, at least 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

26. The polypeptide of Paragraph 24, wherein said polypeptide is obtained from an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

27. The polypeptide of Paragraph 24, wherein said polypeptide is obtained from an organism other than *E. coli*.

28. A purified or isolated polypeptide comprising a polypeptide having at least 25% amino acid identity to a polypeptide whose expression is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, or at least 25% amino acid identity to a fragment comprising at least 10, at least 20, at least 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of a polypeptide whose expression is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 as determined using FASTA version 3.0t78 with the default parameters.

29. The polypeptide of Paragraph 28, wherein said polypeptide has at least 25% identity to a polypeptide comprising one of SEQ ID NOs: 42398-78581 or at least 25% identity to a fragment comprising at least 5, at least 10, at least 20, at least 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of a polypeptide comprising one of SEQ ID NOs.: 42398-78581 as determined using FASTA version 3.0t78 with the default parameters.

30. The polypeptide of Paragraph 28, wherein said polypeptide is obtained from an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

31. The polypeptide of Paragraph 28, wherein said polypeptide is obtained from an organism other than *E. coli*.

32. An antibody capable of specifically binding the polypeptide of one of Paragraphs 28-31.

33. A method of producing a polypeptide, comprising introducing a vector comprising a promoter operably linked to a nucleic acid comprising a nucleotide sequence encoding a polypeptide whose expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-6213 into a cell.

34. The method of Paragraph 33, further comprising the step of isolating said polypeptide.

35. The method of Paragraph 33, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

36. The method of Paragraph 33, wherein said nucleic acid encoding said polypeptide is obtained from an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

37. The method of Paragraph 33, wherein said nucleic acid encoding said polypeptide is obtained from an organism other than *E. coli*.

38. The method of Paragraph 33, wherein said promoter is operably linked to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397.

39. A method of inhibiting proliferation of a cell in an individual comprising inhibiting the activity or reducing the amount of a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 or inhibiting the activity or reducing the amount of a nucleic acid encoding said gene product.

40. The method of Paragraph 39, wherein said method comprises inhibiting said activity or reducing said amount of a gene product in an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia,*

Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica,. Yersinia pestis* and any species falling within the genera of any of the above species.

41. The method of Paragraph 39, wherein said method comprises inhibiting said activity or reducing said amount of a gene product in an organism other than *E. coli*.

42. The method of Paragraph 39, wherein said gene product is present in an organism other than *E. coli*.

43. The method of Paragraph 39, wherein said gene product comprises a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

44. A method for identifying a compound which influences the activity of a gene product required for proliferation, said gene product comprising a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, said method comprising:

contacting said gene product with a candidate compound; and

determining whether said compound influences the activity of said gene product.

45. The method of Paragraph 44, wherein said gene product is from an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis,*

Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis and any species falling within the genera of any of the above species.

46. The method of Paragraph 44, wherein said gene product is from an organism other than *E. coli*.

47. The method of Paragraph 44, wherein said gene product is a polypeptide and said activity is an enzymatic activity.

48. The method of Paragraph 44, wherein said gene product is a polypeptide and said activity is a carbon compound catabolism activity.

49. The method of Paragraph 44, wherein said gene product is a polypeptide and said activity is a biosynthetic activity.

50. The method of Paragraph 44, wherein said gene product is a polypeptide and said activity is a transporter activity.

51. The method of Paragraph 44, wherein said gene product is a polypeptide and said activity is a transcriptional activity.

52. The method of Paragraph 44, wherein said gene product is a polypeptide and said activity is a DNA replication activity.

53. The method of Paragraph 44, wherein said gene product is a polypeptide and said activity is a cell division activity.

54. The method of Paragraph 44, wherein said gene product is an RNA.

55. The method of Paragraph 44, wherein said gene product is a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

56. A compound identified using the method of Paragraph 44.

57. A method for identifying a compound or nucleic acid having the ability to reduce the activity or level of a gene product required for proliferation, said gene product comprising a

gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, said method comprising:

(a) contacting a target gene or RNA encoding said gene product with a candidate compound or nucleic acid; and

(b) measuring an activity of said target.

58. The method of Paragraph 57, wherein said target gene or RNA is from an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

59. The method of Paragraph 57, wherein said target gene or RNA is from an organism other than *E. coli*.

60. The method of Paragraph 57, wherein said gene product is from an organism other than *E. coli*.

61. The method of Paragraph 57, wherein said target is a messenger RNA molecule and said activity is translation of said messenger RNA.

62. The method of Paragraph 57, wherein said target is a messenger RNA molecule and said activity is transcription of a gene encoding said messenger RNA.

63. The method of Paragraph 57, wherein said target is a gene and said activity is transcription of said gene.

64. The method of Paragraph 57, wherein said target is a nontranslated RNA and said activity is processing or folding of said nontranslated RNA or assembly of said nontranslated RNA into a protein/RNA complex.

65. The method of Paragraph 57, wherein said target is a messenger RNA molecule encoding a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

66. The method of Paragraph 57, wherein said target comprises a nucleic acid selected from the group consisting of SEQ ID NOS.: 6214-42397.

67. A compound or nucleic acid identified using the method of Paragraph 57.

68. A method for identifying a compound which reduces the activity or level of a gene product required for proliferation of a cell, wherein the activity or expression of said gene product is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, said method comprising the steps of:

(a) providing a sublethal level of an antisense nucleic acid comprising a nucleotide sequence complementary to a nucleic acid comprising a nucleotide sequence encoding said gene product in a cell to reduce the activity or amount of said gene product in said cell, thereby producing a sensitized cell;

(b) contacting said sensitized cell with a compound; and

(c) determining the degree to which said compound inhibits proliferation of said sensitized cell relative to a cell which does not contain said antisense nucleic acid.

69. The method of Paragraph 68, wherein said determining step comprises determining whether said compound inhibits the growth of said sensitized cell to a greater extent than said compound inhibits the growth of a nonsensitized cell.

70. The method of Paragraph 68, wherein said cell is a Gram positive bacterium.

71. The method of Paragraph 68, wherein said Gram positive bacterium is selected from the group consisting of *Staphylococcus* species, *Streptococcus* species, *Enterococcus* species, *Mycobacterium* species, *Clostridium* species, and *Bacillus* species.

72. The method of Paragraph 68, wherein said bacterium is *Staphylococcus aureus*.

73. The method of Paragraph 72, wherein said *Staphylococcus* species is coagulase negative.

74. The method of Paragraph 72, wherein said bacterium is selected from the group consisting of *Staphylococcus aureus* RN450 and *Staphylococcus aureus* RN4220.

75. The method of Paragraph 68, wherein said cell is an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*),

Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis and any species falling within the genera of any of the above species.

76. The method of Paragraph 68, wherein said cell is not an *E. coli* cell.

77. The method of Paragraph 68, wherein said gene product is from an organism other than *E. coli*.

78. The method of Paragraph 68, wherein said antisense nucleic acid is transcribed from an inducible promoter.

79. The method of Paragraph 68, further comprising the step of contacting said cell with a concentration of inducer which induces transcription of said antisense nucleic acid to a sublethal level.

80. The method of Paragraph 68, wherein growth inhibition is measured by monitoring optical density of a culture growth solution.

81. The method of Paragraph 68, wherein said gene product is a polypeptide.

82. The method of Paragraph 81, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

83. The method of Paragraph 68, wherein said gene product is an RNA.

84. The method of Paragraph 68, wherein nucleic acid encoding said gene product comprises a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397.

85. A compound identified using the method of Paragraph 68.

86. A method for inhibiting cellular proliferation comprising introducing an effective amount of a compound with activity against a gene whose activity or expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 or a compound with activity against the product of said gene into a population of cells expressing said gene.

87. The method of Paragraph 86, wherein said compound is an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, or a proliferation-inhibiting portion thereof.

88. The method of Paragraph 86, wherein said proliferation inhibiting portion of one of SEQ ID NOs.: 1-6213 is a fragment comprising at least 10, at least 20, at least 25, at least 30, at least 50 or more than 51 consecutive nucleotides of one of SEQ ID NOs.: 1-6213.

89. The method of Paragraph 86, wherein said population is a population of Gram positive bacteria.

90. The method of Paragraph 89, wherein said population of Gram positive bacteria is selected from the group consisting of a population of *Staphylococcus* species, *Streptococcus* species, *Enterococcus* species, *Mycobacterium* species, *Clostridium* species, and *Bacillus* species.

91. The method of Paragraph 86, wherein said population is a population of *Staphylococcus aureus*.

92. The method of Paragraph 91, wherein said population is a population of a bacterium selected from the group consisting of *Staphylococcus aureus* RN450 and *Staphylococcus aureus* RN4220.

93. The method of Paragraph 86, wherein said population is a population of a bacterium selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

94. The method of Paragraph 86, wherein said population is a population of an organism other than *E. coli*.

95. The method of Paragraph 86, wherein said product of said gene is from an organism other than *E. coli*.

96. The method of Paragraph 86, wherein said gene encodes a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

97. The method of Paragraph 86, wherein said gene comprises a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397.

98. A composition comprising an effective concentration of an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, or a proliferation-inhibiting portion thereof in a pharmaceutically acceptable carrier.

99. The composition of Paragraph 98, wherein said proliferation-inhibiting portion of one of SEQ ID NOs.: 1-6213 comprises at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive nucleotides of one of SEQ ID NOs.: 1-6213.

100. A method for inhibiting the activity or expression of a gene in an operon required for proliferation wherein the activity or expression of at least one gene in said operon is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-6213, said method comprising contacting a cell in a cell population with an antisense nucleic acid complementary to at least a portion of said operon.

101. The method of Paragraph 100, wherein said antisense nucleic acid comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 or a proliferation-inhibiting portion thereof.

102. The method of Paragraph 100, wherein said cell is selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori,*

Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis and any species falling within the genera of any of the above species.

103. The method of Paragraph 100, wherein said cell is not an *E. coli* cell.

104. The method of Paragraph 100, wherein said gene is from an organism other than *E. coli*.

105. The method of Paragraph 100, wherein said cell is contacted with said antisense nucleic acid by introducing a plasmid which expresses said antisense nucleic acid into said cell population.

106. The method of Paragraph 100, wherein said cell is contacted with said antisense nucleic acid by introducing a phage which encodes said antisense nucleic acid into said cell population.

107. The method of Paragraph 100, wherein said cell is contacted with said antisense nucleic acid by expressing said antisense nucleic acid from the chromosome of cells in said cell population.

108. The method of Paragraph 100, wherein said cell is contacted with said antisense nucleic acid by introducing a promoter adjacent to a chromosomal copy of said antisense nucleic acid such that said promoter directs the transcription of said antisense nucleic acid.

109. The method of Paragraph 100, wherein said cell is contacted with said antisense nucleic acid by introducing a retron which expresses said antisense nucleic acid into said cell population.

110. The method of Paragraph 100, wherein said cell is contacted with said antisense nucleic acid by introducing a ribozyme into said cell-population, wherein a binding portion of said ribozyme comprises said antisense nucleic acid.

111. The method of Paragraph 100, wherein said cell is contacted with said antisense nucleic acid by introducing a liposome comprising said antisense nucleic acid into said cell.

112. The method of Paragraph 100, wherein said cell is contacted with said antisense nucleic acid by electroporation of said antisense nucleic acid into said cell.

113. The method of Paragraph 100, wherein said antisense nucleic acid is a fragment comprising at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive nucleotides of one of SEQ ID NOs.: 1-6213.

114. The method of Paragraph 100 wherein said antisense nucleic acid is a synthetic oligonucleotide.

115. The method of Paragraph 100, wherein said gene comprises a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397.

116. A method for identifying a gene which is required for proliferation of a cell comprising:

(a) contacting a cell with an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, wherein said cell is a cell other than the organism from which said nucleic acid was obtained;

(b) determining whether said nucleic acid inhibits proliferation of said cell; and

(c) identifying the gene in said cell which encodes the mRNA which is complementary to said antisense nucleic acid or a portion thereof.

117. The method of Paragraph 116, wherein said cell is selected from the group consisting of *Staphylococcus* species, *Streptococcus* species, *Enterococcus* species, *Mycobacterium* species, *Clostridium* species, and *Bacillus* species.

118. The method of Paragraph 116 wherein said cell is selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

119. The method of Paragraph 116, wherein said cell is not *E. coli*.

120. The method of Paragraph 116, further comprising operably linking said antisense nucleic acid to a promoter which is functional in said cell, said promoter being included in a vector, and introducing said vector into said cell.

121. A method for identifying a compound having the ability to inhibit proliferation of a cell comprising:

(a) identifying a homolog of a gene or gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs. 1-6213 in a test cell, wherein said test cell is not the cell from which said nucleic acid was obtained;

(b) identifying an inhibitory nucleic acid sequence which inhibits the activity of said homolog in said test cell;

(c) contacting said test cell with a sublethal level of said inhibitory nucleic acid, thus sensitizing said cell;

(d) contacting the sensitized cell of step (c) with a compound; and

(e) determining the degree to which said compound inhibits proliferation of said sensitized cell relative to a cell which does not contain said inhibitory nucleic acid.

122. The method of Paragraph 121, wherein said determining step comprises determining whether said compound inhibits proliferation of said sensitized test cell to a greater extent than said compound inhibits proliferation of a nonsensitized test cell.

123. The method of Paragraph 121, wherein step (a) comprises identifying a nucleic acid homologous to a gene or gene product whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs. 1-6213 or a nucleic acid encoding a homologous polypeptide to a polypeptide whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs. 1-6213 by using an algorithm selected from the group consisting of BLASTN version 2.0 with the default parameters and FASTA version 3.0t78 algorithm with the default parameters to identify said homologous nucleic acid or said nucleic acid encoding a homologous polypeptide in a database.

124. The method of Paragraph 121 wherein said step (a) comprises identifying a homologous nucleic acid or a nucleic acid comprising a sequence of nucleotides encoding a homologous polypeptide by identifying nucleic acids which hybridize to said nucleic acid selected from the group consisting of SEQ ID NOs. 1-6213 or the complement of said nucleic acid selected from the group consisting of SEQ ID NOs. 1-6213.

125. The method of Paragraph 121 wherein step (a) comprises expressing a nucleic acid selected from the group consisting of SEQ ID NOs. 1-6213 in said test cell.

126. The method of Paragraph 121, wherein step (a) comprises identifying a homologous nucleic acid or a nucleic acid encoding a homologous polypeptide in a test cell selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida*

pseudotropicalis), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

127. The method of Paragraph 121, wherein step (a) comprises identifying a homologous nucleic acid or a nucleic acid encoding a homologous polypeptide in a test cell other than *E. coli*.

128. The method of Paragraph 121, wherein said inhibitory nucleic acid is an antisense nucleic acid.

129. The method of Paragraph 121, wherein said inhibitory nucleic acid comprises an antisense nucleic acid to a portion of said homolog.

130. The method of Paragraph 121, wherein said inhibitory nucleic acid comprises an antisense nucleic acid to a portion of the operon encoding said homolog.

131. The method of Paragraph 121, wherein the step of contacting the cell with a sublethal level of said inhibitory nucleic acid comprises directly contacting the surface of said cell with said inhibitory nucleic acid.

132. The method of Paragraph 121, wherein the step of contacting the cell with a sublethal level of said inhibitory nucleic acid comprises transcribing an antisense nucleic acid complementary to at least a portion of the RNA transcribed from said homolog in said cell.

133. The method of Paragraph 121, wherein said gene product comprises a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

134. The method of Paragraph 121, wherein said gene comprises a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397.

135. A compound identified using the method of Paragraph 121.

136. A method of identifying a compound having the ability to inhibit proliferation comprising:

(a) contacting a test cell with a sublethal level of a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs. 1-6213 or a portion thereof which inhibits the proliferation of the cell from which said nucleic acid was obtained, thus sensitizing said test cell;

(b) contacting the sensitized test cell of step (a) with a compound; and

(c) determining the degree to which said compound inhibits proliferation of said sensitized test cell relative to a cell which does not contain said nucleic acid.

137. The method of Paragraph 136, wherein said determining step comprises determining whether said compound inhibits proliferation of said sensitized test cell to a greater extent than said compound inhibits proliferation of a nonsensitized test cell.

138. A compound identified using the method of Paragraph 136.

139. The method of Paragraph 136, wherein said test cell is selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

140. The method of Paragraph 136, wherein the test cell is not *E. coli*.

141. A method for identifying a compound having activity against a biological pathway required for proliferation comprising:

(a) sensitizing a cell by providing a sublethal level of an antisense nucleic acid complementary to a nucleic acid encoding a gene product required for proliferation, wherein the activity or expression of said gene product is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, in said cell to reduce the activity or amount of said gene product;

(b) contacting the sensitized cell with a compound; and

(c) determining the degree to which said compound inhibits the growth of said sensitized cell relative to a cell which does not contain said antisense nucleic acid.

142. The method of Paragraph 141, wherein said determining step comprises determining whether said compound inhibits the growth of said sensitized cell to a greater extent than said compound inhibits the growth of a nonsensitized cell.

143. The method of Paragraph 141, wherein said cell is selected from the group consisting of bacterial cells, fungal cells, plant cells, and animal cells.

144. The method of Paragraph 141, wherein said cell is a Gram positive bacterium.

145. The method of Paragraph 144, wherein said Gram positive bacterium is selected from the group consisting of *Staphylococcus* species, *Streptococcus* species, *Enterococcus* species, *Mycobacterium* species, *Clostridium* species, and *Bacillus* species.

146. The method of Paragraph 145, wherein said Gram positive bacterium is *Staphylococcus aureus*.

147. The method of Paragraph 146, wherein said Gram positive bacterium is selected from the group consisting of *Staphylococcus aureus* RN450 and *Staphylococcus aureus* RN4220.

148. The method of Paragraph 141, wherein said cell is selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella*

typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis and any species falling within the genera of any of the above species.

149. The method of Paragraph 141, wherein said cell is not an *E. coli* cell.

150. The method of Paragraph 141, wherein said gene product is from an organism other than *E. coli*.

151. The method of Paragraph 141, wherein said antisense nucleic acid is transcribed from an inducible promoter.

152. The method of Paragraph 141, further comprising contacting the cell with an agent which induces transcription of said antisense nucleic acid from said inducible promoter, wherein said antisense nucleic acid is transcribed at a sublethal level.

153. The method of Paragraph 141, wherein inhibition of proliferation is measured by monitoring the optical density of a liquid culture.

154. The method of Paragraph 141, wherein said gene product comprises a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

155. The method of Paragraph 141, wherein said nucleic acid encoding said gene product comprises a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397.

156. A compound identified using the method of Paragraph 141.

157. A method for identifying a compound having the ability to inhibit cellular proliferation comprising:

(a) contacting a cell with an agent which reduces the activity or level of a gene product required for proliferation of said cell, wherein said gene product is a gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213;

(b) contacting said cell with a compound; and

(c) determining whether said compound reduces proliferation of said contacted cell by acting on said gene product.

158. The method of Paragraph 157, wherein said determining step comprises determining whether said compound reduces proliferation of said contacted cell to a greater extent than said compound reduces proliferation of cells which have not been contacted with said agent.

159. The method of Paragraph 157, wherein said cell is selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida*

glabrata (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

160. The method of Paragraph 157, wherein said cell is not an *E. coli* cell.

161. The method of Paragraph 157, wherein said gene product is from an organism other than *E. coli*.

162. The method of Paragraph 157, wherein said agent which reduces the activity or level of a gene product required for proliferation of said cell comprises an antisense nucleic acid to a gene or operon required for proliferation.

163. The method of Paragraph 157, wherein said agent which reduces the activity or level of a gene product required for proliferation of said cell comprises a compound known to inhibit growth or proliferation of a cell.

164. The method of Paragraph 157, wherein said cell contains a mutation which reduces the activity or level of said gene product required for proliferation of said cell.

165. The method of Paragraph 157, wherein said mutation is a temperature sensitive mutation.

166. The method of Paragraph 157, wherein said gene product comprises a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

167. A compound identified using the method of Paragraph 157.

168. A method for identifying the biological pathway in which a proliferation-required gene or its gene product lies, wherein said gene or gene product comprises a gene or gene product

whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-6213, said method comprising:

(a) providing a sublethal level of an antisense nucleic acid which inhibits the activity of said proliferation-required gene or gene product in a test cell;

(b) contacting said test cell with a compound known to inhibit growth or proliferation of a cell, wherein the biological pathway on which said compound acts is known; and

(c) determining the degree to which said proliferation of said test cell is inhibited relative to a cell which was not contacted with said compound.

169. The method of Paragraph 168, wherein said determining step comprises determining whether said test cell has a substantially greater sensitivity to said compound than a cell which does not express said sublethal level of said antisense nucleic acid.

170. The method of Paragraph 168, wherein said gene product comprises a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

171. The method of Paragraph 168, wherein said test cell is selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

172. The method of Paragraph 168, wherein said test cell is not an *E. coli* cell.

173. The method of Paragraph 168, wherein said gene product is from an organism other than *E. coli*.

174. A method for determining the biological pathway on which a test compound acts comprising:

(a) providing a sublethal level of an antisense nucleic acid complementary to a proliferation-required nucleic acid in a first cell, wherein the activity or expression of said proliferation-required nucleic acid is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-6213 and wherein the biological pathway in which said proliferation-required nucleic acid or a protein encoded by said proliferation-required nucleic acid lies is known,

(b) contacting said first cell with said test compound; and

(c) determining the degree to which said test compound inhibits proliferation of said first cell relative to a cell which does not contain said antisense nucleic acid.

175. The method of Paragraph 174, wherein said determining step comprises determining whether said first cell has a substantially greater sensitivity to said test compound than a cell which does not express said sublethal level of said antisense nucleic acid.

176. The method of Paragraph 174, further comprising:

(d) providing a sublethal level of a second antisense nucleic acid complementary to a second proliferation-required nucleic acid in a second cell, wherein said second proliferation-required nucleic acid is in a different biological pathway than said proliferation-required nucleic acid in step (a); and

(e) determining whether said second cell does not have a substantially greater sensitivity to said test compound than a cell which does not express said sublethal level of said second antisense nucleic acid, wherein said test compound is specific for the biological pathway against which the antisense nucleic acid of step (a) acts if said first cell has a substantially greater sensitivity to said test compound than said second cell.

177. The method of Paragraph 174, wherein said first cell is selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis,*

Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis and any species falling within the genera of any of the above species.

178. The method of Paragraph 174, wherein said first cell is not an *E. coli* cell.

179. The method of Paragraph 174, wherein said proliferation-required nucleic acid is from an organism other than *E. coli*.

180. A purified or isolated nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-6213.

181. A compound which interacts with a gene or gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence of one of SEQ ID NOs.: 1-6213 to inhibit proliferation.

182. The compound of Paragraph 181, wherein said gene product is a polypeptide comprising one of SEQ ID NOs.: 42398-78581.

183. The compound of Paragraph 181, wherein said gene comprises a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397.

184. A compound which interacts with a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence of one of SEQ ID NOs.: 1-6213 to inhibit proliferation.

185. A method for manufacturing an antibiotic comprising the steps of:

screening one or more candidate compounds to identify a compound that reduces the activity or level of a gene product required for proliferation, said gene product comprising a gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213; and

manufacturing the compound so identified.

186. The method of Paragraph 185, wherein said screening step comprises performing any one of the methods of Paragraphs 44, 68, 121, 136, 141, and 157.

187. The method of Paragraph 185, wherein said gene product is a polypeptide comprising one of SEQ ID NOs:42398-78581.

188. A method for inhibiting proliferation of a cell in a subject comprising administering an effective amount of a compound that reduces the activity or level of a gene product required for proliferation of said cell, said gene product comprising a gene product whose activity or expression

is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 to said subject.

189. The method of Paragraph 188 wherein said subject is selected from the group consisting of vertebrates, mammals, avians, and human beings.

190. The method of Paragraph 188, wherein said gene product comprises a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

191. The method of Paragraph 188, wherein said cell is selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

192. The method of Paragraph 188, wherein said cell is not *E. coli*.

193. The method of Paragraph 188, wherein said gene product is from an organism other than *E. coli*.

194. A purified or isolated nucleic acid consisting essentially of the coding sequence of one of SEQ ID NOs: 6214-42397.

195. A fragment of the nucleic acid of Paragraph 8, said fragment comprising at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive nucleotides of one of SEQ ID NOs: 6214-42397.

196. A purified or isolated nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity to a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, fragments comprising at least 25 consecutive nucleotides of SEQ ID NOs.: 6214-42397, the nucleotide sequences complementary to SEQ ID NOs.:6214-42397, and the nucleotide sequences complementary to fragments comprising at least 25 consecutive nucleotides of SEQ ID NOs.: 6214-42397 as determined using BLASTN version 2.0 with the default parameters.

197. The nucleic acid of Paragraph 196, wherein said nucleic acid is from an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

198. The nucleic acid of Paragraph 196, wherein said nucleic acid is from an organism other than *E. coli*.

199. A method of inhibiting proliferation of a cell comprising inhibiting the activity or reducing the amount of a gene product in said cell or inhibiting the activity or reducing the amount of a nucleic acid encoding said gene product in said cell, wherein said gene product is selected from the group consisting of a gene product having having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at

least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs:1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213.

200. The method of Paragraph 199, wherein said method comprises inhibiting said activity or reducing said amount of said gene product or inhibiting the activity or reducing the amount of a nucleic acid encoding said gene product in an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

201. The method of Paragraph 199, wherein said method comprises inhibiting said activity or reducing said amount of said gene product or inhibiting the activity or reducing the amount of a nucleic acid encoding said gene product in an organism other than *E. coli*.

202. The method of Paragraph 199, wherein said gene product is from an organism other than *E. coli*.

203. The method of Paragraph 199, wherein said gene product comprises a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42398-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42398-78581.

204. The method of Paragraph 199, wherein said gene product is encoded by a nucleic acid selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate condtions.

205. A method for identifying a compound which influences the activity of a gene product required for proliferation comprising:

contacting a candidate compound with a gene product selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs:1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented

by the gene product whose activity is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs: 1-6213; and

determining whether said candidate compound influences the activity of said gene product.

206. The method of Paragraph 205, wherein said gene product is from an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

207. The method of Paragraph 205, wherein said gene product is from an organism other than *E. coli*.

208. The method of Paragraph 205, wherein said gene product is a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42398-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42398-78581.

209. The method of Paragraph 205, wherein said gene product is encoded by a nucleic acid selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid which hybridizes to a sequence selected from the group consisting of SEQ ID

NOS.: 6214-42397 under stringent conditions, and a nucleic acid which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate condtions.

210. A compound identified using the method of Paragraph 205.

211. A method for identifying a compound or nucleic acid having the ability to reduce the activity or level of a gene product required for proliferation comprising:

(a) providing a target that is a gene or RNA, wherein said target comprises a nucleic acid that encodes a gene product selected from the group consisting of a gene product having having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleic acid identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs:1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs: 1-6213;

(b) contacting said target with a candidate compound or nucleic acid; and

(c) measuring an activity of said target.

212. The method of Paragraph 211, wherein said target gene or RNA is from an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila,*

Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis and any species falling within the genera of any of the above species.

213. The method of Paragraph 211, wherein said target gene or RNA is from an organism other than *E. coli*.

214. The method of Paragraph 211, wherein said gene product is from an organism other than *E. coli*.

215. The method of Paragraph 211, wherein said target is a messenger RNA molecule and said activity is translation of said messenger RNA.

216. The method of Paragraph 211, wherein said compound is a nucleic acid and said activity is translation of said gene product.

217. The method of Paragraph 211, wherein said target is a gene and said activity is transcription of said gene.

218. The method of Paragraph 211, wherein said target is a nontranslated RNA and said activity is processing or folding of said nontranslated RNA or assembly of said nontranslated RNA into a protein/RNA complex.

219. The method of Paragraph 211, wherein said target gene is a messenger RNA molecule encoding a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42398-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42398-78581.

220. The method of Paragraph 11, wherein said target gene comprises a nucleic acid selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate condtions.

221. A compound or nucleic acid identified using the method of Paragraph 211.

222. A method for identifying a compound which reduces the activity or level of a gene product required for proliferation of a cell comprising:

(a) providing a sublethal level of an antisense nucleic acid complementary to a nucleic acid encoding said gene product in a cell to reduce the activity or amount of said gene product in said cell, thereby producing a sensitized cell, wherein said gene product is selected from the group consisting of a gene product having having at least 70% nucleic acid identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs:1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs: 1-6213;

(b) contacting said sensitized cell with a compound; and

(c) determining the degree to which said compound inhibits the growth of said sensitized cell relative to a cell which does not contain said antisense nucleic acid.

223. The method of Paragraph 222, wherein said determining step comprises determining whether said compound inhibits the growth of said sensitized cell to a greater extent than said compound inhibits the growth of a nonsensitized cell.

224. The method of Paragraph 222, wherein said sensitized cell is a Gram positive bacterium.

225. The method of Paragraph 224, wherein said Gram positive bacterium is selected from the group consisting of *Staphylococcus* species, *Streptococcus* species, *Enterococcus* species, *Mycobacterium* species, *Clostridium* species, and *Bacillus* species.

226. The method of Paragraph 225, wherein said bacterium is *Staphylococcus aureus*.

227. The method of Paragraph 224, wherein said *Staphylococcus* species is coagulase negative.

228. The method of Paragraph 226, wherein said bacterium is selected from the group consisting of *Staphylococcus aureus* RN450 and *Staphylococcus aureus* RN4220.

229. The method of Paragraph 222, wherein said sensitized cell is an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

230. The method of Paragraph 222, wherein said cell is an organism other than *E. coli*.

231. The method of Paragraph 222, wherein said gene product is from an organism other than *E. coli*.

232. The method of Paragraph 222, wherein said antisense nucleic acid is transcribed from an inducible promoter.

233. The method of Paragraph 222, further comprising the step of contacting said cell with a concentration of inducer which induces transcription of said antisense nucleic acid to a sublethal level.

234. The method of Paragraph 222, wherein growth inhibition is measured by monitoring optical density of a culture medium.

235. The method of Paragraph 222, wherein said gene product is a polypeptide.

236. The method of Paragraph 235, wherein said polypeptide comprises a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of

SEQ ID NOs.: 42398-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42398-78581.

237. The method of Paragraph 222, wherein said gene product is an RNA.

238. The method of Paragraph 222, wherein said nucleic acid encoding said gene product comprises a nucleic acid selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleic acid identity as determined using BLASTN version 2.0 with the default parameters to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate condtions.

239. A compound identified using the method of Paragraph 222.

240. A method for inhibiting cellular proliferation comprising introducing a compound with activity against a gene product or a compound with activity against a gene encoding said gene product into a population of cells expressing said gene product, wherein said gene product is selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs:1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs: 1-6213.

241. The method of Paragraph 240, wherein said compound is an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, or a proliferation-inhibiting portion thereof.

242. The method of Paragraph 240, wherein said proliferation inhibiting portion of one of SEQ ID NOs.: 1-6213 is a fragment comprising at least 10, at least 20, at least 25, at least 30, at least 50 or more than 51 consecutive nucleotides of one of SEQ ID NOs.: 1-6213.

243. The method of Paragraph 240, wherein said population is a population of Gram positive bacteria.

244. The method of Paragraph 243, wherein said population of Gram positive bacteria is selected from the group consisting of a population of *Staphylococcus* species, *Streptococcus* species, *Enterococcus* species, *Mycobacterium* species, *Clostridium* species, and *Bacillus* species.

245. The method of Paragraph 243, wherein said population is a population of *Staphylococcus aureus*.

246. The method of Paragraph 245, wherein said population is a population of a bacterium selected from the group consisting of *Staphylococcus aureus* RN450 and *Staphylococcus aureus* RN4220.

247. The method of Paragraph 240, wherein said population is a population of a bacterium selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

248. The method of Paragraph 240, wherein said population is a population of an organism other than *E. coli*.

249. The method of Paragraph 240, wherein said product of said gene is from an organism other than *E. coli*.

250. The method of Paragraph 240, wherein said gene product is selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using

FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42398-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42398-78581.

251. The method of Paragraph 240, wherein said gene comprises a nucleic acid selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate condtions.

252. A preparation comprising an effective concentration of an antisense nucleic acid in a pharmaceutically acceptable carrier wherein said antisense nucleic acid is selected from the group consisting of a nucleic acid comprising a sequence having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 or a proliferation-inhibiting portion thereof, a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions.

253. The preparation of Paragraph 252, wherein said proliferation-inhibiting portion of one of SEQ ID NOs.: 1-6213 comprises at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive nucleotides of one of SEQ ID NOs.: 1-6213.

254. A method for inhibiting the activity or expression of a gene in an operon which encodes a gene product required for proliferation comprising contacting a cell in a cell population with an antisense nucleic acid comprising at least a proliferation-inhibiting portion of said operon in an antisense orientation, wherein said gene product is selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs:1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the

group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs: 1-6213.

255. The method of Paragraph 254, wherein said antisense nucleic acid comprises a nucleotide sequence having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide seqence selected from the group consisting of SEQ ID NOs.: 1-6213, a proliferation inhibiting portion thereof, a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, and a nucleic acid which comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions.

256. The method of Paragraph 254, wherein said cell is selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

257. The method of Paragraph 254, wherein said cell is not an *E. coli* cell.

258. The method of Paragraph 254, wherein said gene is from an organism other than *E. coli*.

259. The method of Paragraph 254, wherein said cell is contacted with said antisense nucleic acid by introducing a plasmid which transcribes said antisense nucleic acid into said cell population.

260. The method of Paragraph 254, wherein said cell is contacted with said antisense nucleic acid by introducing a phage which transcribes said antisense nucleic acid into said cell population.

261. The method of Paragraph 254, wherein said cell is contacted with said antisense nucleic acid by transcribing said antisense nucleic acid from the chromosome of cells in said cell population.

262. The method of Paragraph 254, wherein said cell is contacted with said antisense nucleic acid by introducing a promoter adjacent to a chromosomal copy of said antisense nucleic acid such that said promoter directs the synthesis of said antisense nucleic acid.

263. The method of Paragraph 254, wherein said cell is contacted with said antisense nucleic acid by introducing a retron which expresses said antisense nucleic acid into said cell population.

264. The method of Paragraph 254, wherein said cell is contacted with said antisense nucleic acid by introducing a ribozyme into said cell-population, wherein a binding portion of said ribozyme is complementary to said antisense oligonucleotide.

265. The method of Paragraph 254, wherein said cell is contacted with said antisense nucleic acid by introducing a liposome comprising said antisense oligonucleotide into said cell.

266. The method of Paragraph 254, wherein said cell is contacted with said antisense nucleic acid by electroporation of said antisense nucleic acid into said cell.

267. The method of Paragraph 254, wherein said antisense nucleic acid has at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence comprising at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive nucleotides of one of SEQ ID NOs.: 1-6213.

268. The method of Paragraph 254 wherein said antisense nucleic acid is a synthetic oligonucleotide.

269. The method of Paragraph 254, wherein said gene comprises a nucleic acid selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate condtions.

270. A method for identifying a gene which is required for proliferation of a cell comprising:

(a) contacting a cell with an antisense nucleic acid selected from the group consisting of a nucleic acid at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 or a proliferation-inhibiting portion thereof, a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, wherein said cell is a cell other than the organism from which said nucleic acid was obtained;

(b) determining whether said nucleic acid inhibits proliferation of said cell; and

(c) identifying the gene in said cell which encodes the mRNA which is complementary to said antisense nucleic acid or a portion thereof.

271. The method of Paragraph 270, wherein said cell is selected from the group consisting of *Staphylococcus* species, *Streptococcus* species, *Enterococcus* species, *Mycobacterium* species, *Clostridium* species, and *Bacillus* species.

272. The method of Paragraph 270 wherein said cell is selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

273. The method of Paragraph 270, wherein said cell is not *E. coli*.

274. The method of Paragraph 270, further comprising operably linking said antisense nucleic acid to a promoter which is functional in said cell, said promoter being included in a vector, and introducing said vector into said cell.

275. A method for identifying a compound having the ability to inhibit proliferation of a cell comprising:

(a) identifying a homolog of a gene or gene product whose activity or level is inhibited by an antisense nucleic acid in a test cell, wherein said test cell is not the microorgaism from which the antisense nucleic acid was obtained, wherein said antisense nucleic acid is selected from the group consisting of a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOs. 1-6213, a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions;

(b) identifying an inhibitory nucleic acid sequence which inhibits the activity of said homolog in said test cell;

(c) contacting said test cell with a sublethal level of said inhibitory nucleic acid, thus sensitizing said cell;

(d) contacting the sensitized cell of step (c) with a compound; and

(e) determining the degree to which said compound inhibits proliferation of said sensitized cell relative to a cell which does not express said inhibitory nucleic acid.

276. The method of Paragraph 275, wherein said determining step comprises determining whether said compound inhibits proliferation of said sensitized test cell to a greater extent than said compound inhibits proliferation of a nonsensitized test cell.

277. The method of Paragraph 275, wherein step (a) comprises identifying a homologous nucleic acid to a gene or gene product whose activity or level is inhibited by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOs. 1-6213 or a nucleic acid encoding a homologous polypeptide to a polypeptide whose activity or level is inhibited by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOs. 1-6213 by using an algorithm selected from the group consisting of BLASTN version 2.0 with the default parameters and FASTA version 3.0t78 algorithm with the default parameters to identify said homologous nucleic acid or said nucleic acid encoding a homologous polypeptide in a database.

278. The method of Paragraph 275 wherein said step (a) comprises identifying a homologous nucleic acid or a nucleic acid encoding a homologous polypeptide by identifying

nucleic acids comprising nucleotide sequences which hybridize to said nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOs. 1-6213 or the complement of the nucleotide sequence of said nucleic acid selected from the group consisting of SEQ ID NOs. 1-6213.

279. The method of Paragraph 275 wherein step (a) comprises expressing a nucleic acid having at least 70% nucleic acid identity as determined using BLASTN version 2.0 with the default parameters to a sequence selected from the group consisting of SEQ ID NOs. 1-6213 in said test cell.

280. The method of Paragraph 275, wherein step (a) comprises identifying a homologous nucleic acid or a nucleic acid encoding a homologous polypeptide in an test cell selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

281. The method of Paragraph 275, wherein step (a) comprises identifying a homologous nucleic acid or a nucleic acid encoding a homologous polypeptide in a test cell other than *E. coli*.

282. The method of Paragraph 275, wherein said inhibitory nucleic acid is an antisense nucleic acid.

283. The method of Paragraph 275, wherein said inhibitory nucleic acid comprises an antisense nucleic acid to a portion of said homolog.

284. The method of Paragraph 275, wherein said inhibitory nucleic acid comprises an antisense nucleic acid to a portion of the operon encoding said homolog.

285. The method of Paragraph 275, wherein the step of contacting the cell with a sublethal level of said inhibitory nucleic acid comprises directly contacting said cell with said inhibitory nucleic acid.

286. The method of Paragraph 275, wherein the step of contacting the cell with a sublethal level of said inhibitory nucleic acid comprises expressing an antisense nucleic acid to said homolog in said cell.

287. The method of Paragraph 275, wherein said gene product comprises a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

288. The method of Paragraph 275, wherein said gene comprises a nucleic acid selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate condtions.

289. A compound identified using the method of Paragraph 275.

290. A method of identifying a compound having the ability to inhibit proliferation comprising:

(a) sensitizing a test cell by contacting said test cell with a sublethal level of an antisense nucleic acid, wherein said antisense nucleic acid is selected from the group consisting of a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOs. 1-6213 or a portion thereof which inhibits the proliferation of the cell from which said nucleic acid was obtained, a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditionst;

(b) contacting the sensitized test cell of step (a) with a compound; and

(c) determining the degree to which said compound inhibits proliferation of said sensitized test cell relative to a cell which does not contain said antisense nucleic acid.

291. The method of Paragraph 290, wherein said determining step comprises determining whether said compound inhibits proliferation of said sensitized test cell to a greater extent than said compound inhibits proliferation of a nonsensitized test cell.

292. A compound identified using the method of Paragraph 290.

293. The method of Paragraph 290, wherein said test cell is selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

294. The method of Paragraph 290, wherein the test cell is not *E. coli*.

295. A method for identifying a compound having activity against a biological pathway required for proliferation comprising:

(a) sensitizing a cell by providing a sublethal level of an antisense nucleic acid complementary to a nucleic acid encoding a gene product required for proliferation, wherein said gene product is selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid

comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs:1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs: 1-6213;

(b) contacting the sensitized cell with a compound; and

(c) determining the extent to which said compound inhibits the growth of said sensitized cell relative to a cell which does not contain said antisense nucleic acid.

296. The method of Paragraph 295, wherein said determining step comprises determining whether said compound inhibits the growth of said sensitized cell to a greater extent than said compound inhibits the growth of a nonsensitized cell.

297. The method of Paragraph 295, wherein said cell is selected from the group consisting of bacterial cells, fungal cells, plant cells, and animal cells.

298. The method of Paragraph 295, wherein said cell is a Gram positive bacterium.

299. The method of Paragraph 298, wherein said Gram positive bacterium is selected from the group consisting of *Staphylococcus* species, *Streptococcus* species, *Enterococcus* species, *Mycobacterium* species, *Clostridium* species, and *Bacillus* species.

300. The method of Paragraph 299, wherein said Gram positive bacterium is *Staphylococcus aureus*.

301. The method of Paragraph 298, wherein said Gram positive bacterium is selected from the group consisting of *Staphylococcus aureus* RN450 and *Staphylococcus aureus* RN4220.

302. The method of Paragraph 295, wherein said cell is selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria*

monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis and any species falling within the genera of any of the above species.

303. The method of Paragraph 295, wherein said cell is not an *E. coli* cell.

304. The method of Paragraph 295, wherein said gene product is from an organism other than *E. coli*.

305. The method of Paragraph 295, wherein said antisense nucleic acid is transcribed from an inducible promoter.

306. The method of Paragraph 305, further comprising contacting the cell with an agent which induces expression of said antisense nucleic acid from said inducible promoter, wherein said antisense nucleic acid is expressed at a sublethal level.

307. The method of Paragraph 295, wherein inhibition of proliferation is measured by monitoring the optical density of a liquid culture.

308. The method of Paragraph 295, wherein said gene product comprises a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

309. The method of Paragraph 295, wherein said nucleic acid encoding said gene product comprises a nucleic acid selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate condtions.

310. A compound identified using the method of Paragraph 295.

311. A method for identifying a compound having the ability to inhibit cellular proliferation comprising:

(a) contacting a cell with an agent which reduces the activity or level of a gene product required for proliferation of said cell, wherein said gene product is selected from

the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs:1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs: 1-6213;

(b) contacting said cell with a compound; and

(c) determining the degree to which said compound reduces proliferation of said contacted cell relative to a cell which was not contacted with said agent.

312. The method of Paragraph 311, wherein said determining step comprises determining whether said compound reduces proliferation of said contacted cell to a greater extent than said compound reduces proliferation of cells which have not been contacted with said agent.

313. The method of Paragraph 311, wherein said cell is selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella*

haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis and any species falling within the genera of any of the above species.

314. The method of Paragraph 311, wherein said cell is not an *E. coli* cell.

315. The method of Paragraph 311, wherein said gene product is from an organism other than *E. coli*.

316. The method of Paragraph 311, wherein said agent which reduces the activity or level of a gene product required for proliferation of said cell comprises an antisense nucleic acid to a gene or operon required for proliferation.

317. The method of Paragraph 311, wherein said agent which reduces the activity or level of a gene product required for proliferation of said cell comprises a compound known to inhibit growth or proliferation of a cell.

318. The method of Paragraph 311, wherein said cell contains a mutation which reduces the activity or level of said gene product required for proliferation of said cell.

319. The method of Paragraph 311, wherein said mutation is a temperature sensitive mutation.

320. The method of Paragraph 311, wherein said gene product comprises a gene product comprises a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

321. A compound identified using the method of Paragraph 311.

322. A method for identifying the biological pathway in which a proliferation-required gene product or a gene encoding a proliferation-required gene product lies comprising:

(a) providing a sublethal level of an antisense nucleic acid which inhibits the activity or reduces the level of said gene encoding a proliferation-required gene product or said said proliferation-required gene product in a test cell, wherein said proliferation-required gene product is selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid

comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs:1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs: 1-6213;

(b) contacting said test cell with a compound known to inhibit growth or proliferation of a cell, wherein the biological pathway on which said compound acts is known; and

(c) determining the degree to which said compound inhibits proliferation of said test cell relative to a cell which does not contain said antisense nucleic acid.

323. The method of Paragraph 322, wherein said determining step comprises determining whether said test cell has a substantially greater sensitivity to said compound than a cell which does not express said sublethal level of said antisense nucleic acid.

324. The method of Paragraph 322, wherein said gene product comprises a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

325. The method of Paragraph 322, wherein said test cell is selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris,*

Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis and any species falling within the genera of any of the above species.

326. The method of Paragraph 322, wherein said test cell is not an *E. coli* cell.

327. The method of Paragraph 322, wherein said gene product is from an organism other than *E. coli.*

328. A method for determining the biological pathway on which a test compound acts comprising:

(a) providing a sublethal level of an antisense nucleic acid complementary to a proliferation-required nucleic acid in a cell, thereby producing a sensitized cell, wherein said antisense nucleic acid is selected from the group consisting of a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOs:1-6213 or a proliferation-inhibiting portion thereof,a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions and wherein the biological pathway in which said proliferation-required nucleic acid or a protein encoded by said proliferation-required polypeptide lies is known,

(b) contacting said cell with said test compound; and

(c) determining the degree to which said compound inhibits proliferation of said sensitized cell relative to a cell which does not contain said antisense nucleic acid.

329. The method of Paragraph 328, wherein said determining step comprises determining whether said sensitized cell has a substantially greater sensitivity to said test compound than a cell which does not express said sublethal level of said antisense nucleic acid.

330. The method of Paragraph 328, further comprising:

(d) providing a sublethal level of a second antisense nucleic acid complementary to a second proliferation-required nucleic acid in a second cell, wherein said second proliferation-required nucleic acid is in a different biological pathway than said proliferation-required nucleic acid in step (a); and

(e) determining whether said second cell does not have a substantially greater sensitivity to said test compound than a cell which does not express said sublethal level of said second antisense nucleic acid, wherein said test compound is specific for the biological

pathway against which the antisense nucleic acid of step (a) acts if said sensitized cell has substantially greater sensitivity to said test compound than said second cell.

331. The method of Paragraph 328, wherein said sensitized cell is selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

332. The method of Paragraph 328, wherein said sensitized cell is not an *E. coli* cell.

333. The method of Paragraph 328, wherein said proliferation-required nucleic acid is from an organism other than *E. coli*.

334. A compound which inhibits proliferation by interacting with a gene encoding a gene product required for proliferation or with a gene product required for proliferation, wherein said gene product is selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs:1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product

whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs: 1-6213.

335. The compound of Paragraph 334, wherein said gene product comprises a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

336. The compound of Paragraph 334, wherein said gene comprises a nucleic acid selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate condtions.

337. A method for manufacturing an antibiotic comprising the steps of:

screening one or more candidate compounds to identify a compound that reduces the activity or level of a gene product required for proliferation wherein said gene product is selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs:1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the

gene product whose activity is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs: 1-6213 ; and

manufacturing the compound so identified.

338. The method of Paragraph 337, wherein said screening step comprises performing any one of the methods of Paragraphs 205, 211, 222, 275, 290, 295, 311.

339. The method of Paragraph 337, wherein said gene product comprises a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

340. A method for inhibiting proliferation of a cell in a subject comprising administering an effective amount of a compound that reduces the activity or level of a gene product required for proliferation of said cell, wherein said gene product is selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs:1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs: 1-6213.

341. The method of Paragraph 340 wherein said subject is selected from the group consisting of vertebrates, mammals, avians, and human beings.

342. The method of Paragraph 340, wherein said gene product comprises a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

343. The method of Paragraph 340, wherein said cell is selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida*

glabrata (also called *Torulopsis glabrata*), *Candida tropicalis*, *Candida parapsilosis*, *Candida guilliermondii*, *Candida krusei*, *Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis*, *Chlamydia pneumoniae*, *Chlamydia trachomatis*, *Clostridium acetobutylicum*, *Clostridium botulinum*, *Clostridium difficile*, *Clostridium perfringens*, *Coccidioides immitis*, *Corynebacterium diptheriae*, *Cryptococcus neoformans*, *Enterobacter cloacae*, *Enterococcus faecalis*, *Enterococcus faecium*, *Escherichia coli*, *Haemophilus influenzae*, *Helicobacter pylori*, *Histoplasma capsulatum*, *Klebsiella pneumoniae*, *Legionella pneumophila*, *Listeria monocytogenes*, *Moraxella catarrhalis*, *Mycobacterium avium*, *Mycobacterium bovis*, *Mycobacterium leprae*, *Mycobacterium tuberculosis*, *Mycoplasma genitalium*, *Mycoplasma pneumoniae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Nocardia asteroides*, *Pasteurella haemolytica*, *Pasteurella multocida*, *Pneumocystis carinii*, *Proteus mirabilis*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Pseudomonas putida*, *Pseudomonas syringae*, *Salmonella bongori*, *Salmonella cholerasuis*, *Salmonella enterica*, *Salmonella paratyphi*, *Salmonella typhi*, *Salmonella typhimurium*, *Shigella boydii*, *Shigella dysenteriae*, *Shigella flexneri*, *Shigella sonnei*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *Streptococcus pneumoniae*, *Streptococcus mutans*, *Streptococcus pyogenes*, *Treponema pallidum*, *Ureaplasma urealyticum*, *Vibrio cholerae*, *Vibrio parahaemolyticus*, *Vibrio vulnificans*, *Yersinia enterocolitica*, *Yersinia pestis* and any species falling within the genera of any of the above species.

344. The method of Paragraph 340, wherein said cell is not *E. coli*.

345. The method of Paragraph 340, wherein said gene product is from an organism other than *E. coli*.

346. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain in said culture overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 is overexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which do not overexpress said gene product on which said compound acts, such that strains which overexpress said gene product on which said compound acts proliferate more rapidly than strains which do not overexpress said gene product on which said compound acts; and

identifying the gene product which is overexpressed in a strain which proliferated more rapidly in said culture.

347. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain in said culture overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397 is overexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which do not overexpress said gene product on which said compound acts, such that strains which overexpress said gene product on which said compound acts proliferate more rapidly than strains which do not overexpress said gene product on which said compound acts; and

identifying the gene product which is overexpressed in a strain which proliferated more rapidly in said culture.

348. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain in said culture overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581 is overexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which do not overexpress said gene product on which said compound acts, such that strains which overexpress said gene product on which said compound acts proliferate more rapidly than strains which do not overexpress said gene product on which said compound acts; and

identifying the gene product which is overexpressed in a strain which proliferated more rapidly in said culture.

349. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain in said culture overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide

sequence selected from the group consisting of SEQ ID NOs: 1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213 is overexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which do not overexpress said gene product on which said compound acts, such that strains which overexpress said gene product on which said compound acts proliferate more rapidly than strains which do not overexpress said gene product on which said compound acts; and

identifying the gene product which is overexpressed in a strain which proliferated more rapidly in said culture.

350. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain in said culture overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate conditions is overexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which do not overexpress said gene product on which said compound acts, such that strains which overexpress said gene product on which said compound acts proliferate more rapidly than strains which do not overexpress said gene product on which said compound acts; and

identifying the gene product which is overexpressed in a strain which proliferated more rapidly in said culture.

351. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain in said culture overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product comprises a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42938-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is overexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which do not overexpress said gene product on which said compound acts, such that strains which overexpress said gene product on which said compound acts proliferate more rapidly than strains which do not overexpress said gene product on which said compound acts; and

identifying the gene product which is overexpressed in a strain which proliferated more rapidly in said culture.

352. The method of Paragraph 346, 347, 348, 349, 350 or 351, wherein said culture includes at least one strain which does not overexpresses a gene product which is essential for proliferation of said organism.

353. The method of Paragraph 346, 347, 348, 349, 350 or 351, wherein said strains which overexpress said gene products comprise a nucleic acid encoding said gene product which is essential for proliferation of said organism operably linked to a regulatable promoter.

354. The method of Paragraph 346, 347, 348, 349, 350 or 351, wherein said strains which overexpress said gene products a nucleic acid encoding said gene product which is essential for proliferation of said organism operably linked to a constitutive promoter.

355. The method of Paragraph 346, 347, 348, 349, 350 or 351, wherein said identification step comprises determining the nucleotide sequence of a nucleic acid encoding said gene product in said cell which proliferated more rapidly in said culture.

356. The method of Paragraph 346, 347, 348, 349, 350 or 351, wherein said identification step comprises performing an amplification reaction to identify the nucleic acid encoding said gene product in said cell which proliferated more rapidly in said cell culture.

357. The method of Paragraph 356, wherein the products of said amplification reaction are labeled with a detectable dye.

358. The method of Paragraph 346, 347, 348, 349, 350 or 351, wherein said identification step comprises performing a hybridization procedure.

359. The method of Paragraph 346, 347, 348, 349, 350 or 351, wherein said identification step comprises contacting a nucleic acid array with a nucleic acid encoding said gene product in said cell which proliferated more rapidly in said cell culture.

360. The method of Paragraph 346, 347, 348, 349, 350 or 351, wherein said organism is selected from the group consisting of bacteria, fungi, and protozoa.

361. The method of Paragraph 346, 347, 348, 349, 350 or 351, wherein said culture is a culture of an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

362. The method of Paragraph 346, 347, 348, 349, 350 or 351, wherein said compound is obtained from a library of natural compounds.

363. The method of Paragraph 346, 347, 348, 349, 350 or 351, wherein said compound is obtained from a library of synthetic compounds.

364. The method of Paragraph 346, 347, 348, 349, 350 or 351, wherein said compound is present in a crude or partially purified state.

365. The method of Paragraph 346, 347, 348, 349, 350 or 351, further comprising determining whether said gene product in said strain which proliferated more rapidly in said culture has a counterpart in at least one other organism.

366. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining an array of strains on a solid growth medium wherein each strain overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 is overexpressed;

contacting said array of strains with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which do not overexpress said gene product on which said compound acts, such that strains which overexpress said gene product on which said compound acts proliferate more rapidly than strains which do not overexpress said gene product on which said compound acts; and

identifying the gene product which is overexpressed in a strain which proliferated more rapidly on said solid medium.

367. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining an array of strains on a solid growth medium wherein each strain overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397 is overexpressed;

contacting said array of strains with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which do not overexpress said gene product on which said compound acts, such that strains which overexpress said gene product on which said compound acts proliferate more rapidly than strains which do not overexpress said gene product on which said compound acts; and

identifying the gene product which is overexpressed in a strain which proliferated more rapidly on said solid medium.

368. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining an array of strains on a solid growth medium wherein each strain overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581 is overexpressed;

contacting said array of strains with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which do not overexpress said gene product on which said compound acts, such that strains which overexpress said gene product on which said compound acts proliferate more rapidly than strains which do not overexpress said gene product on which said compound acts; and

identifying the gene product which is overexpressed in a strain which proliferated more rapidly on said solid medium.

369. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining an array of strains on a solid growth medium wherein each strain overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213 is overexpressed;

contacting said array of strains with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which do not overexpress said gene product on which said compound acts, such that strains which overexpress said gene product on which said compound acts proliferate more rapidly than strains which do not overexpress said gene product on which said compound acts; and

identifying the gene product which is overexpressed in a strain which proliferated more rapidly on said solid medium.

370. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining an array of strains on a solid growth medium wherein each strain overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of a nucleic acid

comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate conditions is overexpressed;

contacting said array of strains with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which do not overexpress said gene product on which said compound acts, such that strains which overexpress said gene product on which said compound acts proliferate more rapidly than strains which do not overexpress said gene product on which said compound acts; and

identifying the gene product which is overexpressed in a strain which proliferated more rapidly on said solid medium.

371. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining an array of strains on a solid growth medium wherein each strain overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product comprises a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42938-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is overexpressed;

contacting said array of strains with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which do not overexpress said gene product on which said compound acts, such that strains which overexpress said gene product on which said compound acts proliferate more rapidly than strains which do not overexpress said gene product on which said compound acts; and

identifying the gene product which is overexpressed in a strain which proliferated more rapidly on said solid medium.

372. The method of Paragraph 366, 367, 368, 369, 370 or 371, wherein at least one strain in said array does not overexpresses a gene product which is essential for proliferation of said organism.

373. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a plurality of cultures, wherein each culture comprises a plurality of strains wherein each strain overexpresses a different gene product which is essential for

proliferation of said organism, wherein said culture comprises a strain in which a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 is overexpressed;

contacting each of said cultures with a different concentration of said compound; and

identifying the gene product which is overexpressed in a strain whose proliferation is inhibited by said compound.

374. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a plurality of cultures, wherein each culture comprises a plurality of strains wherein each strain overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397 is overexpressed;

contacting each of said cultures with a different concentration of said compound; and

identifying the gene product which is overexpressed in a strain whose proliferation is inhibited by said compound.

375. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a plurality of cultures, wherein each culture comprises a plurality of strains wherein each strain overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581 is overexpressed;

contacting each of said cultures with a different concentration of said compound; and

identifying the gene product which is overexpressed in a strain whose proliferation is inhibited by said compound.

376. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a plurality of cultures, wherein each culture comprises a plurality of strains wherein each strain overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene

product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213 is overexpressed;

contacting each of said cultures with a different concentration of said compound; and

identifying the gene product which is overexpressed in a strain whose proliferation is inhibited by said compound.

377. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a plurality of cultures, wherein each culture comprises a plurality of strains wherein each strain overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate conditions is overexpressed;

contacting each of said cultures with a different concentration of said compound; and

identifying the gene product which is overexpressed in a strain whose proliferation is inhibited by said compound.

378. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a plurality of cultures, wherein each culture comprises a plurality of strains wherein each strain overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product comprises a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42938-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is overexpressed;

contacting each of said cultures with a different concentration of said compound; and

identifying the gene product which is overexpressed in a strain whose proliferation is inhibited by said compound.

379. The method of Paragraph 373, 374, 375, 376, 377 or 378, wherein at least one strain in said plurality of cultures does not overexpress a gene product which is essential for proliferation of said organism.

380. A method of profiling a compound's activity comprising:

performing the method of Paragraph 346 on a first culture using a first compound;

performing the method of Paragraph 346 on a second culture using a second compound; and

comparing the strains identified in said first culture to the strains identified in said second culture.

381. A method of profiling a compound's activity comprising:

performing the method of Paragraph 347 on a first culture using a first compound;

performing the method of Paragraph 347 on a second culture using a second compound; and

comparing the strains identified in said first culture to the strains identified in said second culture.

382. A method of profiling a compound's activity comprising:

performing the method of Paragraph 348 on a first culture using a first compound;

performing the method of Paragraph 348 on a second culture using a second compound; and

comparing the strains identified in said first culture to the strains identified in said second culture.

383. A method of profiling a compound's activity comprising:

performing the method of Paragraph 349 on a first culture using a first compound;

performing the method of Paragraph 349 on a second culture using a second compound; and

comparing the strains identified in said first culture to the strains identified in said second culture.

384. A method of profiling a compound's activity comprising:

performing the method of Paragraph 350 on a first culture using a first compound;

performing the method of Paragraph 350 on a second culture using a second compound; and

comparing the strains identified in said first culture to the strains identified in said second culture.

385. A method of profiling a compound's activity comprising:

performing the method of Paragraph 351 on a first culture using a first compound;

performing the method of Paragraph 351 on a second culture using a second compound; and

comparing the strains identified in said first culture to the strains identified in said second culture.

386. A method of profiling a first compound's activity comprising:

growing an array of strains on a first solid medium comprising said first compound and on a second solid medium comprising a second compound, wherein each strain in said array overexpresses a different gene product which is essential for proliferation of an organism, wherein said culture comprises a strain in which a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 is overexpressed, and wherein said first compound and said second compound inhibit the proliferation of said organism; and

comparing the pattern of strains which grow on said first solid medium with the pattern of strains which grow on said second solid medium.

387. A method of profiling a first compound's activity comprising:

growing an array of strains on a first solid medium comprising said first compound and on a second solid medium comprising a second compound, wherein each strain in said array overexpresses a different gene product which is essential for proliferation of an organism, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397 is overexpressed, and wherein said first compound and said second compound inhibit the proliferation of said organism; and

comparing the pattern of strains which grow on said first solid medium with the pattern of strains which grow on said second solid medium.

388. A method of profiling a first compound's activity comprising:

growing an array of strains on a first solid medium comprising said first compound and on a second solid medium comprising a second compound, wherein each strain in said array overexpresses a different gene product which is essential for proliferation of an organism, wherein said culture comprises a strain in which a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581 is overexpressed, and wherein said first compound and said second compound inhibit the proliferation of said organism; and

comparing the pattern of strains which grow on said first solid medium with the pattern of strains which grow on said second solid medium.

389. A method of profiling a first compound's activity comprising:

growing an array of strains on a first solid medium comprising said first compound and on a second solid medium comprising a second compound, wherein each strain in said array overexpresses a different gene product which is essential for proliferation of an organism, wherein said culture comprises a strain in which a gene product selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213 is overexpressed, and wherein said first compound and said second compound inhibit the proliferation of said organism; and

comparing the pattern of strains which grow on said first solid medium with the pattern of strains which grow on said second solid medium.

390. A method of profiling a first compound's activity comprising:

growing an array of strains on a first solid medium comprising said first compound and on a second solid medium comprising a second compound, wherein each strain in said array overexpresses a different gene product which is essential for proliferation of an organism, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate conditions is overexpressed, and wherein said first compound and said second compound inhibit the proliferation of said organism; and

comparing the pattern of strains which grow on said first solid medium with the pattern of strains which grow on said second solid medium.

391. A method of profiling a first compound's activity comprising:

growing an array of strains on a first solid medium comprising said first compound and on a second solid medium comprising a second compound, wherein each strain in said array overexpresses a different gene product which is essential for proliferation of an organism, wherein said culture comprises a strain in which a gene product comprises a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42938-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is overexpressed, and wherein said first compound and said second compound inhibit the proliferation of said organism; and

comparing the pattern of strains which grow on said first solid medium with the pattern of strains which grow on said second solid medium.

392. The method of any one of Paragraphs 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390 or 391, wherein said first compound is present in a crude or partially purified state.

393. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 is underexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which underexpress said gene product on which said compound acts, such that strains which underexpress said gene product on which said compound acts proliferate more slowly than strains which do not underexpress said gene product on which said compound acts; and

identifying the gene product which is underexpressed in a strain which proliferated more slowly in said culture.

394. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397 is underexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which underexpress said gene product on which said compound acts, such that strains which underexpress said gene product on which said compound acts proliferate more slowly than strains which do not underexpress said gene product on which said compound acts; and

identifying the gene product which is underexpressed in a strain which proliferated more slowly in said culture.

395. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581 is underexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which underexpress said gene product on which said compound acts, such that strains which underexpress said gene product on which said compound acts proliferate more slowly than strains which do not underexpress said gene product on which said compound acts; and

identifying the gene product which is underexpressed in a strain which proliferated more slowly in said culture.

396. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213 is underexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which underexpress said gene product on which said compound acts, such that strains which underexpress said gene product on which said compound acts proliferate more slowly than strains which do not underexpress said gene product on which said compound acts; and

identifying the gene product which is underexpressed in a strain which proliferated more slowly in said culture.

397. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid

comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate conditions is underexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which underexpress said gene product on which said compound acts, such that strains which underexpress said gene product on which said compound acts proliferate more slowly than strains which do not underexpress said gene product on which said compound acts; and

identifying the gene product which is underexpressed in a strain which proliferated more slowly in said culture.

398. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product comprises a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42938-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is underexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which underexpress said gene product on which said compound acts, such that strains which underexpress said gene product on which said compound acts proliferate more slowly than strains which do not underexpress said gene product on which said compound acts; and

identifying the gene product which is underexpressed in a strain which proliferated more slowly in said culture.

399. The method of Paragraph 393, 394, 395, 396, 397 or 398, wherein at least one strain in said culture does not underexpresses a gene product which is essential for proliferation of said organism.

400. The method of Paragraph 393, 394, 395, 396, 397 or 398, wherein said strains which underexpresess said gene products comprise a nucleic acid complementary to at least a portion of a gene encoding said gene product which is essential for proliferation of said organism operably linked to a regulatable promoter.

401. The method of Paragraph 393, 394, 395, 396, 397 or 398, wherein said strains which underexpress said gene products express an antisense nucleic acid complementary to at least

a portion of a gene encoding said gene product which is essential for proliferation of said organism, wherein expression of said antisense nucleic acid reduces expression of said gene product in said strain.

402. The method of Paragraph 393, 394, 395, 396, 397 or 398, wherein said identification step comprises determining the nucleotide sequence of a nucleic acid encoding said gene product in said strain which proliferated more slowly.

403. The method of Paragraph 393, 394, 395, 396, 397 or 398, wherein said identification step comprises performing an amplification reaction to identify the nucleic acid encoding said gene product in said cell which proliferated more slowly.

404. The method of Paragraph 393, 394, 395, 396, 397 or 398, wherein the products of said amplification reaction are labeled with a detectable dye.

405. The method of Paragraph 404, wherein said identification step comprises performing a hybridization procedure.

406. The method of Paragraph 393, 394, 395, 396, 397 or 398, wherein said identification step comprises contacting a nucleic acid array with a nucleic acid encoding said gene product in said cell which proliferated more slowly.

407. The method of Paragraph 393, 394, 395, 396, 397 or 398, wherein said organism is selected from the group consisting of bacteria, fungi, protozoa.

408. The method of Paragraph 393, 394, 395, 396, 397 or 398, wherein said culture is a culture of an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum,*

Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis and any species falling within the genera of any of the above species.

409. The method of Paragraph 393, 394, 395, 396, 397 or 398, wherein said compound is obtained from a library of natural compounds.

410. The method of Paragraph 393, 394, 395, 396, 397 or 398, wherein said compound is obtained from a library of synthetic compounds.

411. The method of Paragraph 393, 394, 395, 396, 397 or 398, wherein said compound is present in a crude or partially purified state.

412. The method of Paragraph 393, 394, 395, 396, 397 or 398, further comprising determining whether said gene product in said strain which proliferated more slowly in said culture has a counterpart in at least one other organism.

413. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a plurality of cultures, each culture comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 is underexpressed;

contacting each of said cultures with a different concentration of said compound; and

identifying the gene product which is underexpressed in a strain whose rate of proliferation is reduced by said compound.

414. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a plurality of cultures, each culture comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397 is underexpressed;

contacting each of said cultures with a different concentration of said compound; and

identifying the gene product which is underexpressed in a strain whose rate of proliferation is reduced by said compound.

415. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a plurality of cultures, each culture comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene

product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581 is underexpressed;

contacting each of said cultures with a different concentration of said compound; and

identifying the gene product which is underexpressed in a strain whose rate of proliferation is reduced by said compound.

416. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a plurality of cultures, each culture comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213 is underexpressed;

contacting each of said cultures with a different concentration of said compound; and

identifying the gene product which is underexpressed in a strain whose rate of proliferation is reduced by said compound.

417. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a plurality of cultures, each culture comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for

proliferation of said organism, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate conditions is underexpressed;

contacting each of said cultures with a different concentration of said compound; and

identifying the gene product which is underexpressed in a strain whose rate of proliferation is reduced by said compound.

418. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a plurality of cultures, each culture comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product comprises a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42938-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is underexpressed;

contacting each of said cultures with a different concentration of said compound; and

identifying the gene product which is underexpressed in a strain whose rate of proliferation is reduced by said compound.

419. A method of profiling a compound's activity comprising:

performing the method of Paragraph 393 on a first culture using a first compound;

performing the method of Paragraph 393 on a second culture using a second compound; and

comparing the strains identified in said first culture to the strains identified in said second culture.

420. A method of profiling a compound's activity comprising:

performing the method of Paragraph 394 on a first culture using a first compound;

performing the method of Paragraph 394 on a second culture using a second compound; and

comparing the strains identified in said first culture to the strains identified in said second culture.

421. A method of profiling a compound's activity comprising:

performing the method of Paragraph 395 on a first culture using a first compound;

performing the method of Paragraph 395 on a second culture using a second compound; and

comparing the strains identified in said first culture to the strains identified in said second culture.

422. A method of profiling a compound's activity comprising

performing the method of Paragraph 396 on a first culture using a first compound;

performing the method of Paragraph 396 on a second culture using a second compound; and

comparing the strains identified in said first culture to the strains identified in said second culture.

423. A method of profiling a compound's activity comprising

performing the method of Paragraph 397 on a first culture using a first compound;

performing the method of Paragraph 397 on a second culture using a second compound; and

comparing the strains identified in said first culture to the strains identified in said second culture.

424. A method of profiling a compound's activity comprising

performing the method of Paragraph 398 on a first culture using a first compound;

performing the method of Paragraph 398 on a second culture using a second compound; and

comparing the strains identified in said first culture to the strains identified in said second culture.

425. A method of profiling a first compound's activity comprising:

growing an array of strains on a first solid medium comprising said first compound and on a second solid medium comprising a second compound, wherein said array comprises a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of an organism, wherein said culture comprises a strain in which a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 is underexpressed, and wherein said first compound and said second compound inhibit the proliferation of said organism; and

comparing the pattern of strains which grow on said first solid medium with the pattern of strains which grow on said second solid medium.

426. A method of profiling a first compound's activity comprising:

growing an array of strains on a first solid medium comprising said first compound and on a second solid medium comprising a second compound, wherein said array comprises a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of an organism, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397 is underexpressed, and wherein said first compound and said second compound inhibit the proliferation of said organism; and

comparing the pattern of strains which grow on said first solid medium with the pattern of strains which grow on said second solid medium.

427. A method of profiling a first compound's activity comprising:

growing an array of strains on a first solid medium comprising said first compound and on a second solid medium comprising a second compound, wherein said array comprises a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of an organism, wherein said culture comprises a strain in which a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581 is underexpressed, and wherein said first compound and said second compound inhibit the proliferation of said organism; and

comparing the pattern of strains which grow on said first solid medium with the pattern of strains which grow on said second solid medium.

428. A method of profiling a first compound's activity comprising:

growing an array of strains on a first solid medium comprising said first compound and on a second solid medium comprising a second compound, wherein said array comprises a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of an organism, wherein said culture comprises a strain in which a gene product selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group

consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213 is underexpressed, and wherein said first compound and said second compound inhibit the proliferation of said organism; and

comparing the pattern of strains which grow on said first solid medium with the pattern of strains which grow on said second solid medium.

429. A method of profiling a first compound's activity comprising:

growing an array of strains on a first solid medium comprising said first compound and on a second solid medium comprising a second compound, wherein said array comprises a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of an organism , wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate conditions is underexpressed, and wherein said first compound and said second compound inhibit the proliferation of said organism; and

comparing the pattern of strains which grow on said first solid medium with the pattern of strains which grow on said second solid medium.

430. A method of profiling a first compound's activity comprising:

growing an array of strains on a first solid medium comprising said first compound and on a second solid medium comprising a second compound, wherein said array comprises a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of an organism, wherein said culture comprises a strain in which a gene product comprises a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42938-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is underexpressed, and wherein said first compound and said second compound inhibit the proliferation of said organism; and

comparing the pattern of strains which grow on said first solid medium with the pattern of strains which grow on said second solid medium.

431. The method of any one of Paragraphs 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429 or 430, wherein said first compound is present in a crude or partially purified state.

432. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a plurality of cultures comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 is underexpressed;

contacting each of said plurality of cultures with a varying concentration of a regulatory agent which regulates the level of expression of said gene products which are essential for proliferation of said organism; and

identifying the gene product which is underexpressed in a strain whose rate of proliferation is reduced by said compound.

433. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a plurality of cultures comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397 is underexpressed;

contacting each of said plurality of cultures with a varying concentration of a regulatory agent which regulates the level of expression of said gene products which are essential for proliferation of said organism; and

identifying the gene product which is underexpressed in a strain whose rate of proliferation is reduced by said compound.

434. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a plurality of cultures comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581 is underexpressed;

contacting each of said plurality of cultures with a varying concentration of a regulatory agent which regulates the level of expression of said gene products which are essential for proliferation of said organism; and

identifying the gene product which is underexpressed in a strain whose rate of proliferation is reduced by said compound.

435. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a plurality of cultures comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213 is underexpressed;

contacting each of said plurality of cultures with a varying concentration of a regulatory agent which regulates the level of expression of said gene products which are essential for proliferation of said organism; and

identifying the gene product which is underexpressed in a strain whose rate of proliferation is reduced by said compound.

436. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a plurality of cultures comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as

determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate conditions is underexpressed;

contacting each of said plurality of cultures with a varying concentration of a regulatory agent which regulates the level of expression of said gene products which are essential for proliferation of said organism; and

identifying the gene product which is underexpressed in a strain whose rate of proliferation is reduced by said compound.

437. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a plurality of cultures comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product comprises a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42938-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is underexpressed;

contacting each of said plurality of cultures with a varying concentration of a regulatory agent which regulates the level of expression of said gene products which are essential for proliferation of said organism; and

identifying the gene product which is underexpressed in a strain whose rate of proliferation is reduced by said compound.

438. A culture comprising a plurality of strains wherein each strain overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 is overexpressed.

439. A culture comprising a plurality of strains wherein each strain overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397 is overexpressed.

440. A culture comprising a plurality of strains wherein each strain overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture

comprises a strain in which a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581 is overexpressed.

441. A culture comprising a plurality of strains wherein each strain overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213 is overexpressed.

442. A culture comprising a plurality of strains wherein each strain overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate conditions is overexpressed.

443. A culture comprising a plurality of strains wherein each strain overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product comprises a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42938-78581

and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is overexpressed.

444. The culture of Paragraph 438, 439, 440, 441, 442 or 443, wherein said strains which overexpresess said gene products comprise a nucleic acid encoding said gene product which is essential for proliferation of said organism operably linked to a regulatable promoter.

445. The culture of Paragraph 438, 439, 440, 441, 442 or 443, wherein said strains which overexpresess said gene products comprise a nucleic acid encoding said gene product which is essential for proliferation of said organism operably linked to a constitutive promoter.

446. The culture of Paragraph 438, 439, 440, 441, 442 or 443, wherein said culture is a culture of an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

447. A culture comprising a a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 is underexpressed.

448. A culture comprising a a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture

comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397 is underexpressed.

449. A culture comprising a a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581 is underexpressed.

450. A culture comprising a a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213 is underexpressed.

451. A culture comprising a a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate conditions is underexpressed.

452. A culture comprising a a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture

comprises a strain in which a gene product comprises a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42938-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is underexpressed.

453. The culture of Paragraph 447, 448, 449, 450, 451 or 452, wherein said strains which underexpress said gene products comprise a nucleic acid encoding said gene product which is essential for proliferation of said organism operably linked to a regulatable promoter.

454. The culture of Paragraph 447, 448, 449, 450, 451 or 452, wherein said strains which underexpress said gene products comprise a nucleic acid encoding said gene product which is essential for proliferation of said organism operably linked to a constitutive promoter.

455. The culture of Paragraph 447, 448, 449, 450, 451 or 452, wherein said culture is a culture of an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

456. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain overexpresses a different gene product which is essential for proliferation of said organism and wherein the nucleotide sequence of each of the overexpressed genes has been altered so

as to include a nucleotide sequence which can be used to generate a unique product corresponding to each of the overexpressed genes, wherein said culture comprises a strain in which a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 is overexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which do not overexpress said gene product on which said compound acts, such that strains which overexpress said gene product on which said compound acts proliferate more rapidly than strains which do not overexpress said gene product on which said compound acts; and

identifying the gene product which is overexpressed in a strain which proliferated more rapidly in said culture by detecting the unique product corresponding to said gene.

457. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain overexpresses a different gene product which is essential for proliferation of said organism and wherein the nucleotide sequence of each of the overexpressed genes has been altered so as to include a nucleotide sequence which can be used to generate a unique product corresponding to each of the overexpressed genes, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397 is overexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which do not overexpress said gene product on which said compound acts, such that strains which overexpress said gene product on which said compound acts proliferate more rapidly than strains which do not overexpress said gene product on which said compound acts; and

identifying the gene product which is overexpressed in a strain which proliferated more rapidly in said culture by detecting the unique product corresponding to said gene.

458. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain overexpresses a different gene product which is essential for proliferation of said organism and wherein the nucleotide sequence of each of the overexpressed genes has been altered so as to include a nucleotide sequence which can be used to generate a unique product corresponding to each of the overexpressed genes, wherein said culture comprises a strain in which a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581 is overexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which do not overexpress said gene product on which said compound acts, such that strains which overexpress said gene product on which said compound acts proliferate more rapidly than strains which do not overexpress said gene product on which said compound acts; and

identifying the gene product which is overexpressed in a strain which proliferated more rapidly in said culture by detecting the unique product corresponding to said gene.

459. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain overexpresses a different gene product which is essential for proliferation of said organism and wherein the nucleotide sequence of each of the overexpressed genes has been altered so as to include a nucleotide sequence which can be used to generate a unique product corresponding to each of the overexpressed genes, wherein said culture comprises a strain in which a gene product selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213 is overexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which do not overexpress said gene product on which said compound acts, such that strains which overexpress said gene product on which said compound acts proliferate more rapidly than strains which do not overexpress said gene product on which said compound acts; and

identifying the gene product which is overexpressed in a strain which proliferated more rapidly in said culture by detecting the unique product corresponding to said gene.

460. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain overexpresses a different gene product which is essential for proliferation of said organism and wherein the nucleotide sequence of each of the overexpressed genes has been altered so as to include a nucleotide sequence which can be used to generate a unique product corresponding to each of the overexpressed genes, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate conditions is overexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which do not overexpress said gene product on which said compound acts, such that strains which overexpress said gene product on which said compound acts proliferate more rapidly than strains which do not overexpress said gene product on which said compound acts; and

identifying the gene product which is overexpressed in a strain which proliferated more rapidly in said culture by detecting the unique product corresponding to said gene.

461. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain overexpresses a different gene product which is essential for proliferation of said organism and wherein the nucleotide sequence of each of the overexpressed genes has been altered so as to include a nucleotide sequence which can be used to generate a unique product corresponding to each of the overexpressed genes, wherein said culture comprises a strain in which a gene product comprises a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42938-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is overexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which do not overexpress said gene product on which said compound acts, such that strains which overexpress said gene product on which said compound acts proliferate more rapidly than strains which do not overexpress said gene product on which said compound acts; and

identifying the gene product which is overexpressed in a strain which proliferated more rapidly in said culture by detecting the unique product corresponding to said gene.

462. The method of Paragraph 456, 457, 458, 459, 460 or 461, wherein the nucleotide sequence of each of the genes encoding an overexpressed gene product has been altered by replacing the native promoters of said genes with promoters which facilitate overexpression of said gene products.

463. The method of Paragraph 456, 457, 458, 459, 460 or 461, wherein the nucleotide sequence of each of the genes encoding an overexpressed gene product has been altered by inserting a regulatory element into the native promoters of said genes with a promoter which facilitates overexpression of said gene products.

464. The method of Paragraph 463, wherein said regulatory element is selected from the group consisting of a regulatable promoter, an operator which is recognized by a repressor, a nucleotide sequence which is recognized by a transcriptional activator, a transcriptional terminator, a nucleotide sequence which introduces a bend in the DNA and an upstream activating sequence.

465. The method of Paragraph 456, 457, 458, 459, 460 or 461, wherein the step of identifying the gene product which is overexpressed in a strain which proliferated more rapidly in said culture by detecting the unique product corresponding to said gene comprises performing an amplification reaction and detecting a unique amplification product corresponding to said gene.

466. The method of Paragraph 462, wherein the native promoter of each of the genes encoding a gene product essential for proliferation is replaced with the same promoter.

467. The method of Paragraph 462, wherein the native promoters of the genes encoding gene products essential for proliferation are replaced with a plurality of promoters selected to give a desired expression level for each gene product.

468. The method of Paragraph 462, wherein said promoters which replaced the native promoters in each strain comprise regulatable promoters.

469. The method of Paragraph 462, wherein said promoters which replaced the native promoters in each strain each strain comprise constitutive promoters.

470. The method of Paragraph 456, 457, 458, 459, 460 or 461, wherein said organism is selected from the group consisting of bacteria, fungi, and protozoa.

471. The method of Paragraph 456, 457, 458, 459, 460 or 461, wherein said culture is a culture of an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei,*

Campylobacter jejuni, Candida albicans, Candida glabrata (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

472. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism and wherein the nucleotide sequence of each of the underexpressed genes has been altered so as to include a nucleotide sequence which can be used to generate a unique product corresponding to each of the underexpressed genes and wherein said culture comprises a strain in which a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 is underexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which underexpress said gene product on which said compound acts, such that strains which underexpress said gene product on which said compound acts proliferate more slowly than strains which do not underexpress the gene product on which said compound acts; and

identifying the gene product which is underexpressed in a strain which proliferated more rapidly in said culture by detecting the unique product corresponding to said gene.

473. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism and wherein the nucleotide sequence of each of the underexpressed genes has been altered so as to include a nucleotide sequence which can be used to generate a unique product corresponding to each of the underexpressed genes and wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397 is underexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which underexpress said gene product on which said compound acts, such that strains which underexpress said gene product on which said compound acts proliferate more slowly than strains which do not underexpress the gene product on which said compound acts; and

identifying the gene product which is underexpressed in a strain which proliferated more rapidly in said culture by detecting the unique product corresponding to said gene.

474. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism and wherein the nucleotide sequence of each of the underexpressed genes has been altered so as to include a nucleotide sequence which can be used to generate a unique product corresponding to each of the underexpressed genes, wherein said culture comprises a strain in which a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581 is underexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which underexpress said gene product on which said compound acts, such that strains which underexpress said gene product on which said compound acts proliferate more slowly than strains which do not underexpress the gene product on which said compound acts; and

identifying the gene product which is underexpressed in a strain which proliferated more rapidly in said culture by detecting the unique product corresponding to said gene.

475. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism and wherein the nucleotide sequence of each of the underexpressed genes has been altered so as to include a nucleotide sequence which can be used to generate a unique product corresponding to each of the underexpressed genes, wherein said culture comprises a strain in which a gene product selected from the group consisting of a gene product having at

least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213 is underexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which underexpress said gene product on which said compound acts, such that strains which underexpress said gene product on which said compound acts proliferate more slowly than strains which do not underexpress the gene product on which said compound acts; and

identifying the gene product which is underexpressed in a strain which proliferated more rapidly in said culture by detecting the unique product corresponding to said gene.

476. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism and wherein the nucleotide sequence of each of the underexpressed genes has been altered so as to include a nucleotide sequence which can be used to generate a unique product corresponding to each of the underexpressed genes, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent

conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate conditions is underexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which underexpress said gene product on which said compound acts, such that strains which underexpress said gene product on which said compound acts proliferate more slowly than strains which do not underexpress the gene product on which said compound acts; and

identifying the gene product which is underexpressed in a strain which proliferated more rapidly in said culture by detecting the unique product corresponding to said gene.

477. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism and wherein the nucleotide sequence of each of the underexpressed genes has been altered so as to include a nucleotide sequence which can be used to generate a unique product corresponding to each of the underexpressed genes , wherein said culture comprises a strain in which a gene product comprises a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42938-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is underexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which underexpress said gene product on which said compound acts, such that strains which underexpress said gene product on which said compound acts proliferate more slowly than strains which do not underexpress the gene product on which said compound acts; and

identifying the gene product which is underexpressed in a strain which proliferated more rapidly in said culture by detecting the unique product corresponding to said gene.

478. The method of Paragraph 472, 473, 474, 475, 476 or 477, wherein the nucleotide sequence of each of the genes encoding an underexpressed gene product has been altered by replacing the native promoters of said genes with promoters which facilitate underexpression of said gene products.

479. The method of Paragraph 472, 473, 474, 475, 476 or 477, wherein the nucleotide sequence of each of the genes encoding an underexpressed gene product has been altered by inserting a regulatory element into the native promoters of said genes with a promoter which facilitates underexpression of said gene products.

480. The method of Paragraph 479, wherein said regulatory element is selected from the group consisting of a regulatable promoter, an operator which is recognized by a repressor, a nucleotide sequence which is recognized by a transcriptional activator, a transcriptional terminator, a nucleotide sequence which introduces a bend in the DNA and an upstream activating sequence.

481. The method of Paragraph 472, 473, 474, 475, 476 or 477, wherein the step of identifying the gene product which is underexpressed in a strain which proliferated more slowly in said culture by detecting the unique product corresponding to said gene comprises performing an amplification reaction and detecting a unique amplification product corresponding to said gene.

482. The method of Paragraph 478, wherein the native promoter of each of the genes encoding a gene product essential for proliferation is replaced with the same promoter.

483. The method of Paragraph 478, wherein the native promoters of the genes encoding gene products essential for proliferation are replaced with a plurality of promoters selected to give a desired expression level for each gene product.

484. The method of Paragraph 478, wherein said promoters which replaced the native promoters in each strain comprise regulatable promoters.

485. The method of Paragraph 478, wherein said promoters which replaced the native promoters in each strain each strain comprise constitutive promoters.

486. The method of Paragraph 472, 473, 474, 475, 476 or 477, wherein said organism is selected from the group consisting of bacteria, fungi, and protozoa.

487. The method of Paragraph 472, 473, 474, 475, 476 or 477, wherein said culture is a culture of an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus,*

Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis and any species falling within the genera of any of the above species.

488. A method for determining the extent to which each of a plurality of strains are present in a culture or collection of strains comprising:

obtaining a nucleic acid sample comprising nucleic acids from a culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains wherein each strain overexpresses or underexpresses a different gene product which is required for proliferation of said organism wherein said culture comprises a strain in which a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 is overexpressed or underexpressed;

performing an amplification reaction using a set of primer pairs which are complementary to nucleotide sequences within or adjacent to the genes which encode said gene products, wherein the members of said set of primer pairs are designed such that each primer pair would yield an amplification product having a length distinguishable from the lengths of the amplification products from the other primer pairs if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains; and

determining the lengths of the amplification products obtained in said amplification reaction.

489. A method for determining the extent to which each of a plurality of strains are present in a culture or collection of strains comprising:

obtaining a nucleic acid sample comprising nucleic acids from a culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains wherein each strain overexpresses or underexpresses a different gene product which is required for proliferation of said organism , wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397 is overexpressed or underexpressed;

performing an amplification reaction using a set of primer pairs which are complementary to nucleotide sequences within or adjacent to the genes which encode said gene products, wherein the members of said set of primer pairs are designed such that each primer pair would yield an amplification product having a length distinguishable from the lengths of the amplification products from the other primer pairs if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains; and

determining the lengths of the amplification products obtained in said amplification reaction.

490. A method for determining the extent to which each of a plurality of strains are present in a culture or collection of strains comprising:

obtaining a nucleic acid sample comprising nucleic acids from a culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains wherein each strain overexpresses or underexpresses a different gene product which is required for proliferation of said organism, wherein said culture comprises a strain in which a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581 is overexpressed or underexpressed;

performing an amplification reaction using a set of primer pairs which are complementary to nucleotide sequences within or adjacent to the genes which encode said gene products, wherein the members of said set of primer pairs are designed such that each primer pair would yield an amplification product having a length distinguishable from the lengths of the amplification products from the other primer pairs if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains; and

determining the lengths of the amplification products obtained in said amplification reaction.

491. A method for determining the extent to which each of a plurality of strains are present in a culture or collection of strains comprising:

obtaining a nucleic acid sample comprising nucleic acids from a culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains wherein each strain overexpresses or underexpresses a different gene product which is required for proliferation of said organism , wherein said culture comprises a strain in which a gene product selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group

consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213 is overexpressed or underexpressed;

performing an amplification reaction using a set of primer pairs which are complementary to nucleotide sequences within or adjacent to the genes which encode said gene products, wherein the members of said set of primer pairs are designed such that each primer pair would yield an amplification product having a length distinguishable from the lengths of the amplification products from the other primer pairs if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains; and

determining the lengths of the amplification products obtained in said amplification reaction.

492. A method for determining the extent to which each of a plurality of strains are present in a culture or collection of strains comprising:

obtaining a nucleic acid sample comprising nucleic acids from a culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains wherein each strain overexpresses or underexpresses a different gene product which is required for proliferation of said organism , wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate conditions is overexpressed or underexpressed;

performing an amplification reaction using a set of primer pairs which are complementary to nucleotide sequences within or adjacent to the genes which encode said gene products, wherein the members of said set of primer pairs are designed such that each primer pair would yield an amplification product having a length distinguishable from the lengths of the amplification products from the other primer pairs if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains; and

determining the lengths of the amplification products obtained in said amplification reaction.

493. A method for determining the extent to which each of a plurality of strains are present in a culture or collection of strains comprising:

obtaining a nucleic acid sample comprising nucleic acids from a culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains wherein each strain overexpresses or underexpresses a different gene product which is required for proliferation of said organism , wherein said culture comprises a strain in which a gene product comprising a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42938-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is overexpressed or underexpressed;

performing an amplification reaction using a set of primer pairs which are complementary to nucleotide sequences within or adjacent to the genes which encode said gene products, wherein the members of said set of primer pairs are designed such that each primer pair would yield an amplification product having a length distinguishable from the lengths of the amplification products from the other primer pairs if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains; and

determining the lengths of the amplification products obtained in said amplification reaction.

494. The method of Paragraph 488, 489, 490, 491, 492 or 493, wherein one member of each primer pair for each of said genes is labeled with a detectable dye.

495. The method of Paragraph 488, 489, 490, 491, 492 or 493, wherein:

said nucleic acid sample is divided into N aliquots; and

said amplification reaction is performed on each aliquot using primer pairs complementary to nucleotide sequences within or adjacent to 1/N of the genes which encode said gene products, wherein one of the members of each primer pair in each aliquot is labeled with a dye and wherein the dyes on the primers in each aliquot are distinguishable from one another.

496. The method of Paragraph 494, further comprising pooling the amplification products from each of the aliquots prior to determining the lengths of the amplification products.

497. The method of Paragraph 488, 489, 490, 491, 492 or 493, wherein the native promoters of said genes which encode said gene products have been replaced with a regulatable promoter and one of the primers in said primer pairs is complementary to a nucleotide sequence within said regulatable promoter.

498. The method of Paragraph 496, wherein the native promoters for each of said genes were replaced with the same regulatable promoter.

499. The method of Paragraph 496, wherein more than one regulatable promoter was used to replace the promoters of said genes such that some of said genes are under the control of a different regulatable promoter.

500. A method for identifying the target of a compound which inhibits the proliferation of an organism comprising:

obtaining a first nucleic acid sample comprising nucleic acids from a first culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains wherein each strain overexpresses or underexpresses a different gene product which is required for proliferation of said organism and wherein said culture or collection of strains has been contacted with said compound;

obtaining a second nucleic acid sample comprising nucleic acids from a second culture or collection of strains wherein said culture or collection of strains comprises the same strains as said first culture or collection of strains wherein said second culture or collection of strains has not been contacted with said compound;

performing a first amplification reaction on said first nucleic acid sample using a set of primer pairs which are complementary to nucleotide sequences within or adjacent to the genes which encode said gene products, wherein the members of said set of primer pairs are designed such that each primer pair would yield an amplification product having a length distinguishable from the lengths of the amplification products from the other primer pairs if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains;

performing a second amplification reaction on said second nucleic acid sample using the same set of primer pairs used in said first amplification reaction;

and comparing the amount of each amplification product in said first amplification reaction to the amount of that amplification product in said second amplification reaction, wherein an increased level of an amplification product in said first amplification reaction relative to said second amplification reaction indicates that the gene product corresponding to said amplification product is the target of said compound if said culture or strain overexpresses said gene products and a decreased level of of an amplification product in said first amplification reaction relative to said second amplification reaction indicates that the gene product corresponding to said amplification product is the target of said compound if said culture or strain overexpresses said gene products, wherein said first and second cultures or collection of strains comprise a strain in which a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 is overexpressed or underexpressed.

501. A method for identifying the target of a compound which inhibits the proliferation of an organism comprising:

obtaining a first nucleic acid sample comprising nucleic acids from a first culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains wherein each strain overexpresses or underexpresses a different gene product which is required for proliferation of said organism and wherein said culture or collection of strains has been contacted with said compound;

obtaining a second nucleic acid sample comprising nucleic acids from a second culture or collection of strains wherein said culture or collection of strains comprises the same strains as said first culture or collection of strains wherein said second culture or collection of strains has not been contacted with said compound;

performing a first amplification reaction on said first nucleic acid sample using a set of primer pairs which are complementary to nucleotide sequences within or adjacent to the genes which encode said gene products, wherein the members of said set of primer pairs are designed such that each primer pair would yield an amplification product having a length distinguishable from the lengths of the amplification products from the other primer pairs if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains;

performing a second amplification reaction on said second nucleic acid sample using the same set of primer pairs used in said first amplification reaction;

and comparing the amount of each amplification product in said first amplification reaction to the amount of that amplification product in said second amplification reaction, wherein an increased level of an amplification product in said first amplification reaction relative to said second amplification reaction indicates that the gene product corresponding to said amplification product is the target of said compound if said culture or strain overexpresses said gene products and a decreased level of of an amplification product in said first amplification reaction relative to said second amplification reaction indicates that the gene product corresponding to said amplification product is the target of said compound if said culture or strain overexpresses said gene products, wherein said first and second cultures or collection of strains comprise a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397 is overexpressed or underexpressed.

502. A method for identifying the target of a compound which inhibits the proliferation of an organism comprising:

obtaining a first nucleic acid sample comprising nucleic acids from a first culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains wherein each strain overexpresses or underexpresses a different gene product which

is required for proliferation of said organism and wherein said culture or collection of strains has been contacted with said compound;

obtaining a second nucleic acid sample comprising nucleic acids from a second culture or collection of strains wherein said culture or collection of strains comprises the same strains as said first culture or collection of strains wherein said second culture or collection of strains has not been contacted with said compound;

performing a first amplification reaction on said first nucleic acid sample using a set of primer pairs which are complementary to nucleotide sequences within or adjacent to the genes which encode said gene products, wherein the members of said set of primer pairs are designed such that each primer pair would yield an amplification product having a length distinguishable from the lengths of the amplification products from the other primer pairs if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains;

performing a second amplification reaction on said second nucleic acid sample using the same set of primer pairs used in said first amplification reaction;

and comparing the amount of each amplification product in said first amplification reaction to the amount of that amplification product in said second amplification reaction, wherein an increased level of an amplification product in said first amplification reaction relative to said second amplification reaction indicates that the gene product corresponding to said amplification product is the target of said compound if said culture or strain overexpresses said gene products and a decreased level of of an amplification product in said first amplification reaction relative to said second amplification reaction indicates that the gene product corresponding to said amplification product is the target of said compound if said culture or strain overexpresses said gene products, wherein said first and second cultures or collection of strains comprise a strain in which a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581 is overexpressed or underexpressed.

503. A method for identifying the target of a compound which inhibits the proliferation of an organism comprising:

obtaining a first nucleic acid sample comprising nucleic acids from a first culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains wherein each strain overexpresses or underexpresses a different gene product which is required for proliferation of said organism and wherein said culture or collection of strains has been contacted with said compound;

obtaining a second nucleic acid sample comprising nucleic acids from a second culture or collection of strains wherein said culture or collection of strains comprises the same strains as said first culture or collection of strains wherein said second culture or collection of strains has not been contacted with said compound;

performing a first amplification reaction on said first nucleic acid sample using a set of primer pairs which are complementary to nucleotide sequences within or adjacent to the genes which encode said gene products, wherein the members of said set of primer pairs are designed such that each primer pair would yield an amplification product having a length distinguishable from the lengths of the amplification products from the other primer pairs if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains;

performing a second amplification reaction on said second nucleic acid sample using the same set of primer pairs used in said first amplification reaction;

and comparing the amount of each amplification product in said first amplification reaction to the amount of that amplification product in said second amplification reaction, wherein an increased level of an amplification product in said first amplification reaction relative to said second amplification reaction indicates that the gene product corresponding to said amplification product is the target of said compound if said culture or strain overexpresses said gene products and a decreased level of of an amplification product in said first amplification reaction relative to said second amplification reaction indicates that the gene product corresponding to said amplification product is the target of said compound if said culture or strain overexpresses said gene products, wherein said first and second cultures or collection of strains comprise a strain in which a gene product selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213 is overexpressed or underexpressed.

504. A method for identifying the target of a compound which inhibits the proliferation of an organism comprising:

obtaining a first nucleic acid sample comprising nucleic acids from a first culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains wherein each strain overexpresses or underexpresses a different gene product which is required for proliferation of said organism and wherein said culture or collection of strains has been contacted with said compound;

obtaining a second nucleic acid sample comprising nucleic acids from a second culture or collection of strains wherein said culture or collection of strains comprises the same strains as said first culture or collection of strains wherein said second culture or collection of strains has not been contacted with said compound;

performing a first amplification reaction on said first nucleic acid sample using a set of primer pairs which are complementary to nucleotide sequences within or adjacent to the genes which encode said gene products, wherein the members of said set of primer pairs are designed such that each primer pair would yield an amplification product having a length distinguishable from the lengths of the amplification products from the other primer pairs if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains;

performing a second amplification reaction on said second nucleic acid sample using the same set of primer pairs used in said first amplification reaction;

and comparing the amount of each amplification product in said first amplification reaction to the amount of that amplification product in said second amplification reaction, wherein an increased level of an amplification product in said first amplification reaction relative to said second amplification reaction indicates that the gene product corresponding to said amplification product is the target of said compound if said culture or strain overexpresses said gene products and a decreased level of of an amplification product in said first amplification reaction relative to said second amplification reaction indicates that the gene product corresponding to said amplification product is the target of said compound if said culture or strain overexpresses said gene products, wherein said first and second cultures or collection of strains comprise a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from

the group consisting of SEQ ID NOS.: 6214-42397 under moderate conditions is overexpressed or underexpressed.

505. A method for identifying the target of a compound which inhibits the proliferation of an organism comprising:

obtaining a first nucleic acid sample comprising nucleic acids from a first culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains wherein each strain overexpresses or underexpresses a different gene product which is required for proliferation of said organism and wherein said culture or collection of strains has been contacted with said compound;

obtaining a second nucleic acid sample comprising nucleic acids from a second culture or collection of strains wherein said culture or collection of strains comprises the same strains as said first culture or collection of strains wherein said second culture or collection of strains has not been contacted with said compound;

performing a first amplification reaction on said first nucleic acid sample using a set of primer pairs which are complementary to nucleotide sequences within or adjacent to the genes which encode said gene products, wherein the members of said set of primer pairs are designed such that each primer pair would yield an amplification product having a length distinguishable from the lengths of the amplification products from the other primer pairs if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains;

performing a second amplification reaction on said second nucleic acid sample using the same set of primer pairs used in said first amplification reaction;

and comparing the amount of each amplification product in said first amplification reaction to the amount of that amplification product in said second amplification reaction, wherein an increased level of an amplification product in said first amplification reaction relative to said second amplification reaction indicates that the gene product corresponding to said amplification product is the target of said compound if said culture or strain overexpresses said gene products and a decreased level of of an amplification product in said first amplification reaction relative to said second amplification reaction indicates that the gene product corresponding to said amplification product is the target of said compound if said culture or strain overexpresses said gene products, wherein said first and second culture or collection of strains comprise a strain in which a gene product comprising a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42938-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is overexpressed or underexpressed.

506. The method of Paragraph 500, 501, 502, 503, 504 or 505, wherein one member of each primer pair for each of said genes is labeled with a detectable dye.

507. The method of Paragraph 500, 501, 502, 503, 504 or 505, wherein the native promoters of said genes which encode said gene products have been replaced with a regulatable promoter and one of the primers in said primer pairs is complementary to a nucleotide sequence within said regulatable promoter.

508. The method of Paragraph 500, 501, 502, 503, 504 or 505, wherein the native promoters for each of said genes were replaced with the same regulatable promoter.

509. The method of Paragraph 500, 501, 502, 503, 504 or 505, wherein more than one regulatable promoter was used to replace the promoters of said genes such that some of said genes are under the control of a different regulatable promoter.

510. A method for determining the extent to which each of a plurality of strains are present in a culture or collection of strains comprising:

obtaining a nucleic acid sample comprising nucleic acids from a culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains which transcribe an antisense nucleic acid complementary to a different gene product which is required for proliferation of said organism;

performing an amplification reaction using a set of primer pairs which are complementary to nucleotide sequences within or adjacent to the nucleic acids which encode said antisense nucleic acids, wherein the members of said set of primer pairs are designed such that each primer pair would yield an amplification product having a length distinguishable from the lengths of the amplification products from the other primer pairs if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains; and

determining the lengths of the amplification products obtained in said amplification reaction, wherein said culture comprises a strain in which a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 is overexpressed or underexpressed.

511. A method for determining the extent to which each of a plurality of strains are present in a culture or collection of strains comprising:

obtaining a nucleic acid sample comprising nucleic acids from a culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains which transcribe an antisense nucleic acid complementary to a different gene product which is required for proliferation of said organism;

performing an amplification reaction using a set of primer pairs which are complementary to nucleotide sequences within or adjacent to the nucleic acids which encode said antisense nucleic acids, wherein the members of said set of primer pairs are designed such that each primer pair would yield an amplification product having a length

distinguishable from the lengths of the amplification products from the other primer pairs if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains; and

determining the lengths of the amplification products obtained in said amplification reaction, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397 is overexpressed or underexpressed.

512. A method for determining the extent to which each of a plurality of strains are present in a culture or collection of strains comprising:

obtaining a nucleic acid sample comprising nucleic acids from a culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains which transcribe an antisense nucleic acid complementary to a different gene product which is required for proliferation of said organism;

performing an amplification reaction using a set of primer pairs which are complementary to nucleotide sequences within or adjacent to the nucleic acids which encode said antisense nucleic acids, wherein the members of said set of primer pairs are designed such that each primer pair would yield an amplification product having a length distinguishable from the lengths of the amplification products from the other primer pairs if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains; and

determining the lengths of the amplification products obtained in said amplification reaction, wherein said culture comprises a strain in which a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581 is overexpressed or underexpressed.

513. A method for determining the extent to which each of a plurality of strains are present in a culture or collection of strains comprising:

obtaining a nucleic acid sample comprising nucleic acids from a culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains which transcribe an antisense nucleic acid complementary to a different gene product which is required for proliferation of said organism;

performing an amplification reaction using a set of primer pairs which are complementary to nucleotide sequences within or adjacent to the nucleic acids which encode said antisense nucleic acids, wherein the members of said set of primer pairs are designed such that each primer pair would yield an amplification product having a length distinguishable from the lengths of the amplification products from the other primer pairs if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains; and

determining the lengths of the amplification products obtained in said amplification reaction, wherein said culture comprises a strain in which a gene product selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213 is overexpressed or underexpressed.

514. A method for determining the extent to which each of a plurality of strains are present in a culture or collection of strains comprising:

obtaining a nucleic acid sample comprising nucleic acids from a culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains which transcribe an antisense nucleic acid complementary to a different gene product which is required for proliferation of said organism;

performing an amplification reaction using a set of primer pairs which are complementary to nucleotide sequences within or adjacent to the nucleic acids which encode said antisense nucleic acids, wherein the members of said set of primer pairs are designed such that each primer pair would yield an amplification product having a length distinguishable from the lengths of the amplification products from the other primer pairs if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains; and

determining the lengths of the amplification products obtained in said amplification reaction, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as

determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate conditions is overexpressed or underexpressed.

515. A method for determining the extent to which each of a plurality of strains are present in a culture or collection of strains comprising:

obtaining a nucleic acid sample comprising nucleic acids from a culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains which transcribe an antisense nucleic acid complementary to a different gene product which is required for proliferation of said organism;

performing an amplification reaction using a set of primer pairs which are complementary to nucleotide sequences within or adjacent to the nucleic acids which encode said antisense nucleic acids, wherein the members of said set of primer pairs are designed such that each primer pair would yield an amplification product having a length distinguishable from the lengths of the amplification products from the other primer pairs if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains; and

determining the lengths of the amplification products obtained in said amplification reaction, wherein said culture comprises a strain in which a gene product comprising a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42938-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is overexpressed or underexpressed.

516. The method of Paragraph 510, 511, 512, 513, 514 or 515, wherein one member of each primer pair for each of said genes is labeled with a detectable dye.

517. The method of Paragraph 510, 511, 512, 513, 514 or 515, wherein:

said nucleic acid sample is divided into N aliquots; and

said amplification reaction is performed on each aliquot using primer pairs complementary to nucleotide sequences within or adjacent to 1/N of the genes which encode said gene products, wherein one of the members of each primer pair in each aliquot is labeled with a dye and wherein the dyes on the primers in each aliquot are distinguishable from one another.

518. The method of Paragraph 517, further comprising pooling the amplification products from each of the aliquots prior to determining the lengths of the amplification products.

519. A method for determining the extent to which each of a plurality of strains are present in a culture or collection of strains comprising:

obtaining a nucleic acid sample comprising nucleic acids from a culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains which overexpress or underexpress a different gene product which is required for proliferation of said organism;

performing an amplification reaction using primer pairs which are complementary to nucleotide sequences within or adjacent to the genes which encode said gene products, wherein said primer pairs are designed such that each primer pair would yield an amplification product which is distinguishable from the amplification products produced by the other primer pairs on the a basis selected from the group consisting of length, detectable label and both length and detectable label if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains; and

identifying the amplification products obtained in said amplification reaction, wherein said culture comprises a strain in which a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 is overexpressed or underexpressed.

520. A method for determining the extent to which each of a plurality of strains are present in a culture or collection of strains comprising:

obtaining a nucleic acid sample comprising nucleic acids from a culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains which overexpress or underexpress a different gene product which is required for proliferation of said organism;

performing an amplification reaction using primer pairs which are complementary to nucleotide sequences within or adjacent to the genes which encode said gene products, wherein said primer pairs are designed such that each primer pair would yield an amplification product which is distinguishable from the amplification products produced by the other primer pairs on the a basis selected from the group consisting of length, detectable label and both length and detectable label if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains; and

identifying the amplification products obtained in said amplification reaction, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397 is overexpressed or underexpressed.

521. A method for determining the extent to which each of a plurality of strains are present in a culture or collection of strains comprising:

obtaining a nucleic acid sample comprising nucleic acids from a culture or collection of strains wherein said culture or collection of strains comprises a plurality of

strains which overexpress or underexpress a different gene product which is required for proliferation of said organism;

performing an amplification reaction using primer pairs which are complementary to nucleotide sequences within or adjacent to the genes which encode said gene products, wherein said primer pairs are designed such that each primer pair would yield an amplification product which is distinguishable from the amplification products produced by the other primer pairs on the a basis selected from the group consisting of length, detectable label and both length and detectable label if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains; and

identifying the amplification products obtained in said amplification reaction, wherein said culture comprises a strain in which a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581 is overexpressed or underexpressed.

522. A method for determining the extent to which each of a plurality of strains are present in a culture or collection of strains comprising:

obtaining a nucleic acid sample comprising nucleic acids from a culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains which overexpress or underexpress a different gene product which is required for proliferation of said organism;

performing an amplification reaction using primer pairs which are complementary to nucleotide sequences within or adjacent to the genes which encode said gene products, wherein said primer pairs are designed such that each primer pair would yield an amplification product which is distinguishable from the amplification products produced by the other primer pairs on the a basis selected from the group consisting of length, detectable label and both length and detectable label if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains; and

identifying the amplification products obtained in said amplification reaction, wherein said culture comprises a strain in which a gene product selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide

sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213 is overexpressed or underexpressed.

523. A method for determining the extent to which each of a plurality of strains are present in a culture or collection of strains comprising:

obtaining a nucleic acid sample comprising nucleic acids from a culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains which overexpress or underexpress a different gene product which is required for proliferation of said organism;

performing an amplification reaction using primer pairs which are complementary to nucleotide sequences within or adjacent to the genes which encode said gene products, wherein said primer pairs are designed such that each primer pair would yield an amplification product which is distinguishable from the amplification products produced by the other primer pairs on the a basis selected from the group consisting of length, detectable label and both length and detectable label if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains; and

identifying the amplification products obtained in said amplification reaction, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate conditions is overexpressed or underexpressed.

524. A method for determining the extent to which each of a plurality of strains are present in a culture or collection of strains comprising:

obtaining a nucleic acid sample comprising nucleic acids from a culture or collection of strains wherein said culture or collection of strains comprises a plurality of

strains which overexpress or underexpress a different gene product which is required for proliferation of said organism;

performing an amplification reaction using primer pairs which are complementary to nucleotide sequences within or adjacent to the genes which encode said gene products, wherein said primer pairs are designed such that each primer pair would yield an amplification product which is distinguishable from the amplification products produced by the other primer pairs on the a basis selected from the group consisting of length, detectable label and both length and detectable label if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains; and

identifying the amplification products obtained in said amplification reaction, wherein said culture comprises a strain in which a gene product comprising a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42938-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is overexpressed or underexpressed.

525. The method of Paragraph 519, 520, 521, 522, 523 or 524, wherein said primer pairs are divided into at least two sets, each primer pair comprises a primer which is labeled with a distinguishable dye, and the distinguishable dye used to label each set of primer pairs is distinguishable from the dye used to label the other sets of primer pairs.

526. The method of Paragraph 519, 520, 521, 522, 523 or 524, wherein:

said nucleic acid sample is divided into N aliquots; and

said amplification reaction is performed on each aliquot using primer pairs complementary to nucleotide sequences within or adjacent to 1/N of the genes which encode said gene products, wherein one of the members of each primer pair in each aliquot is labeled with a dye and wherein the dyes on the primers in each aliquot are distinguishable from one another.

527. The method of Paragraph 526, further comprising pooling the amplification products from each of the aliquots prior to determining the lengths of the amplification products.

528. The method of Paragraph 519, 520, 521, 522, 523 or 524, wherein the native promoters of said genes which encode said gene products have been replaced with a regulatable promoter and one of the primers in said primer pairs is complementary to a nucleotide sequence within said regulatable promoter.

529. The method of Paragraph 528, wherein the native promoters for each of said genes were replaced with the same regulatable promoter.

530. The method of Paragraph 528, wherein more than one regulatable promoter was used to replace the promoters of said genes such that some of said genes are under the control of a different regulatable promoter.

Definitions

By "biological pathway" is meant any discrete cell function or process that is carried out by a gene product or a subset of gene products. Biological pathways include anabolic, catabolic, enzymatic, biochemical and metabolic pathways as well as pathways involved in the production of cellular structures such as cell walls. Biological pathways that are usually required for proliferation of cells or microorganisms include, but are not limited to, cell division, DNA synthesis and replication, RNA synthesis (transcription), protein synthesis (translation), protein processing, protein transport, fatty acid biosynthesis, electron transport chains, cell wall synthesis, cell membrane production, synthesis and maintenance, and the like.

By "inhibit activity of a gene or gene product" is meant having the ability to interfere with the function of a gene or gene product in such a way as to decrease expression of the gene, in such a way as to reduce the level or activity of a product of the gene or in such a way as to inhibit the interaction of the gene or gene product with other biological molecules required for its activity. Agents which inhibit the activity of a gene include agents that inhibit transcription of the gene, agents that inhibit processing of the transcript of the gene, agents that reduce the stability of the transcript of the gene, and agents that inhibit translation of the mRNA transcribed from the gene. In microorganisms, agents which inhibit the activity of a gene can act to decrease expression of the operon in which the gene resides or alter the folding or processing of operon RNA so as to reduce the level or activity of the gene product. The gene product can be a non-translated RNA such as ribosomal RNA, a translated RNA (mRNA) or the protein product resulting from translation of the gene mRNA. Of particular utility to the present invention are antisense RNAs that have activities against the operons or genes to which they specifically hybridze.

By "activity against a gene product" is meant having the ability to inhibit the function or to reduce the level or activity of the gene product in a cell. This includes, but is not limited to, inhibiting the enzymatic activity of the gene product or the ability of the gene product to interact with other biological molecules required for its activity, including inhibiting the gene product's assembly into a multimeric structure.

By "activity against a protein" is meant having the ability to inhibit the function or to reduce the level or activity of the protein in a cell. This includes, but is not limited to, inhibiting the enzymatic activity of the protein or the ability of the protein to interact with other biological molecules required for its activity, including inhibiting the protein's assembly into a multimeric structure.

By "activity against a nucleic acid" is meant having the ability to inhibit the function or to reduce the level or activity of the nucleic acid in a cell. This includes, but is not limited to, inhibiting the ability of the nucleic acid interact with other biological molecules required for its activity, including inhibiting the nucleic acid's assembly into a multimeric structure.

By "activity against a gene" is meant having the ability to inhibit the function or expression of the gene in a cell. This includes, but is not limited to, inhibiting the ability of the gene to interact with other biological molecules required for its activity.

By "activity against an operon" is meant having the ability to inhibit the function or reduce the level of one or more products of the operon in a cell. This includes, but is not limited to, inhibiting the enzymatic activity of one or more products of the operon or the ability of one or more products of the operon to interact with other biological molecules required for its activity.

By "antibiotic" is meant an agent which inhibits the proliferation of a cell or microorganism.

By "*E. coli or Escherichia coli*" is meant *Escherichia coli* or any organism previously categorized as a species of *Shigella* including *Shigella boydii, Shigella flexneri, Shigella dysenteriae, Shigella sonnei, Shigella 2A.*

By "homologous coding nucleic acid" is meant a nucleic acid homologous to a nucleic acid encoding a gene product whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 or a portion thereof. In some embodiments, the homologous coding nucleic acid may have at least 97%, at least 95%, at least 90%, at least 85%, at least 80%, or at least 70% nucleotide sequence identity to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42,397 and fragments comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides thereof. In other embodiments the homologous coding nucleic acids may have at least 97%, at least 95%, at least 90%, at least 85%, at least 80%, or at least 70% nucleotide sequence identity to a nucleotide sequence selected from the group consisting of the nucleotide sequences complementary to one of SEQ ID NOs.: 1-6213 and fragments comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides thereof. Identity may be measured using BLASTN version 2.0 with the default parameters or tBLASTX with the default parameters. (Altschul, S.F. et al. Gapped BLAST and PSI-BLAST: A New Generation of Protein Database Search Programs, Nucleic Acid Res. 25: 3389-3402 (1997). Alternatively a "homologuous coding nucleic acid" could be identified by membership of the gene of interest to a functional orthologue cluster. All other members of that orthologue cluster would be considered homologues. Such a library of functional orthologue clusters can be found at http://www.ncbi.nlm.nih.gov/COG. A gene can be classified into a cluster of orthologous groups or COG by using the COGNITOR program available at the above web site, or by direct BLASTP comparison of the gene of interest to the members of the COGs and analysis of these results as described by Tatusov, R.L., Galperin, M.Y., Natale, D. A. and Koonin, E.V. (2000) The COG database: a tool for genome-scale analysis of protein functions and evolution. Nucleic Acids Research v. 28 n. 1, pp33-36.

Homologous coding nucleic acids and the homologous polypeptides which they encode may also be identified using a "reciprocal" best-hit analysis. To facilitate the identification of homologous coding nucleic acids and homologous polypeptides, paralogous genes within each of

51 organisms are identified and clustered prior to comparison to other organisms. Briefly, the polypeptide sequence of each polypeptide encoded by each open reading frame (ORF) in a given organism is compared to the polypeptide sequence encoded by every other ORF for that organism for each of the 51 pathogenic organisms (PathoSeq Sept 2001 release) using BLASTP 2.09 algorithm without filtering. Simultaneously, the polypeptide sequence encoded by each ORF of an organism is compared to the polypeptide sequences encoded by each of the ORFs in the remaining 51 organisms. Those polypeptides within a single organism that shared a higher degree of sequence identity to one another than to polypeptide sequences obtained from any other organisms are clustered as "paralog" sequences for "reciprocal" best-hit analysis.

For each reference organism, the 50 homologous coding nucleic acids (and the 50 homologous polypeptides which they encode) can be determined by identifying the ORFs in each of the 50 comparison organisms which encode a polypeptide sharing the highest degree of amino acid sequence identity to the polypeptide encoded by the ORF from the reference organism. The accuracy of the identification of the predicted homologous coding nucleic acids (and the homologous polypeptides which they encode) is confirmed by a "reciprocal" BLAST analysis in which the polypeptide sequence of the predicted homologous polypeptide is compared against the polypeptides encoded by each of the ORFS in the reference organism using BLASTP 2.09 algorithm without filtering. Only those polypeptides that share the highest degree of amino acid sequence identity in each portion of the two-way comparison are retained for further analysis.

The term "homologous coding nucleic acid" also includes nucleic acids comprising nucleotide sequences which encode polypeptides having at least 99%, 95%, at least 90%, at least 85%, at least 80%, at least 70%, at least 60%, at least 50%, at least 40% or at least 25% maino acid identity or similarity to a polypeptide comprising the amino acid sequence of one of SEQ ID NOs: 42,398-78,581 or to a polypeptpide whose expression is inhibited by a nucleic acid comprising a nucleotide sequence of one of SEQ ID NOs: 1-6213 or fragments comprising at least 5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, or 150 consecutive amino acids thereof as determined using the FASTA version 3.0t78 algorithm with the default parameters. Alternatively, protein identity or similarity may be identified using BLASTP with the default parameters, BLASTX with the default parameters, TBLASTN with the default parameters, or tBLASTX with the default parameters. (Altschul, S.F. et al. Gapped BLAST and PSI-BLAST: A New Generation of Protein Database Search Programs, Nucleic Acid Res. 25: 3389-3402 (1997).

Additionally, homologous coding nucleic acids and the homologous polypeptides which they encode may be identified using a "reciprocal" best-hit analysis. To facilitate the identification of homologous coding nucleic acids and homologous polypeptides, paralogous genes within each of 51 organisms are identified and clustered prior to comparison to other organisms. Briefly, the polypeptide sequence of each polypeptide encoded by each open reading frame (ORF) in a given organism is compared to the polypeptide sequence encoded by every other ORF for that organism for each of the 51 pathogenic organisms (PathoSeq Sept 2001 release) using BLASTP 2.09

algorithm without filtering. Simultaneously, the polypeptide sequence encoded by each ORF of an organism is compared to the polypeptide sequences encoded by each of the ORFs in the remaining 51 organisms. Those polypeptides within a single organism that shared a higher degree of sequence identity to one another than to polypeptide sequences obtained from any other organisms are clustered as "paralog" sequences for "reciprocal" best-hit analysis.

For each reference organism, the 50 homologous coding nucleic acids (and the 50 homologous polypeptides which they encode) can be determined by identifying the ORFs in each of the 50 comparison organisms which encode a polypeptide sharing the highest degree of amino acid sequence identity to the polypeptide encoded by the ORF from the reference organism. The accuracy of the identification of the predicted homologous coding nucleic acids (and the homologous polypeptides which they encode) is confirmed by a "reciprocal" BLAST analysis in which the polypeptide sequence of the predicted homologous polypeptide is compared against the polypeptides encoded by each of the ORFS in the reference organism using BLASTP 2.09 algorithm without filtering. Only those polypeptides that share the highest degree of amino acid sequence identity in each portion of the two-way comparison are retained for further analysis.

The term "homologous coding nucleic acid" also includes coding nucleic acids which hybridize under stringent conditions to a nucleic acid selected from the group consisting of the nucleotide sequences complementary to one of SEQ ID NOS.: 6214-42,397 and coding nucleic acids comprising nucleotide sequences which hybridize under stringent conditions to a fragment comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of the sequences complementary to one of SEQ ID NOS.: 6214-42,397. As used herein, "stringent conditions" means hybridization to filter-bound nucleic acid in 6xSSC at about 45°C followed by one or more washes in 0.1xSSC/0.2% SDS at about 68°C. Other exemplary stringent conditions may refer, *e.g.*, to washing in 6xSSC/0.05% sodium pyrophosphate at 37°C, 48°C, 55°C, and 60°C as appropriate for the particular probe being used.

The term "homologous coding nucleic acid" also includes coding nucleic acids comprising nucleotide sequences which hybridize under moderate conditions to a nucleotide sequence selected from the group consisting of the sequences complementary to one of SEQ ID NOS.: 6214-42,397 and coding nucleic acids comprising nucleotide sequences which hybridize under moderate conditions to a fragment comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of the sequences complementary to one of SEQ ID NOS.: 6214-42,397. As used herein, "moderate conditions" means hybridization to filter-bound DNA in 6x sodium chloride/sodium citrate (SSC) at about 45°C followed by one or more washes in 0.2xSSC/0.1% SDS at about 42-65°C.

The term "homologous coding nucleic acids" also includes nucleic acids comprising nucleotide sequences which encode a gene product whose activity may be complemented by a gene encoding a gene product whose activity is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213. In some embodiments, the

homologous coding nucleic acids may encode a gene product whose activity is complemented by the gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42,397. In other embodiments, the homologous coding nucleic acids may comprise a nucleotide sequence encode a gene product whose activity is complemented by one of the polypeptides of SEQ ID NOs. 42,398-78,581.

The term "homologous antisense nucleic acid" includes nucleic acids comprising a nucleotide sequence having at least 97%, at least 95%, at least 90%, at least 85%, at least 80%, or at least 70% nucleotide sequence identity to a nucleotide sequence selected from the group consisting of one of the sequences of SEQ ID NOS. 1-6213 and fragments comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides thereof. Homologous antisense nucleic acids may also comprising nucleotide sequences which have at least 97%, at least 95%, at least 90%, at least 85%, at least 80%, or at least 70% nucleotide sequence identity to a nucleotide sequence selected from the group consisting of the sequences complementary to one of sequences of SEQ ID NOS.: 6214-42,397 and fragments comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides thereof. Nucleic acid identity may be determined as described above.

The term "homologous antisense nucleic acid" also includes antisense nucleic acids comprising nucleotide sequences which hybridize under stringent conditions to a nucleotide sequence complementary to one of SEQ ID NOs.: 1-6213 and antisense nucleic acids comprising nucleotide sequences which hybridize under stringent conditions to a fragment comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of the sequence complementary to one of SEQ ID NOs. 1-6213. Homologous antisense nucleic acids also include antisense nucleic acids comprising nucleotide sequences which hybridize under stringent conditions to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42,397 and antisense nucleic acids comprising nucleotide sequences which hybridize under stringent conditions to a fragment comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of one of SEQ ID NOS.: 6214-42,397.

The term "homologous antisense nucleic acid" also includes antisense nucleic acids comprising nucleotide sequences which hybridize under moderate conditions to a nucleotide sequence complementary to one of SEQ ID NOs.: 1-6213 and antisense nucleic acids comprising nucleotide seuqences which hybridize under moderate conditions to a fragment comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of the sequence complementary to one of SEQ ID NOs. 1-6213. Homologous antisense nucleic acids also include antisense nucleic acids comprising nucleotide seuqences which hybridize under moderate conditions to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42,397 and antisense nucleic acids which comprising nucleotide sequences hybridize under moderate conditions to a fragment comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of one of SEQ ID NOS.: 6214-42,397.

By "homologous polypeptide" is meant a polypeptide homologous to a polypeptide whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 or by a homologous antisense nucleic acid. The term "homologous polypeptide" includes polypeptides having at least 99%, 95%, at least 90%, at least 85%, at least 80%, at least 70%, at least 60%, at least 50%, at least 40% or at least 25% amino acid identity or similarity to a polypeptide whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs: 1-6213 or by a homologous antisense nucleic acid, or polypeptides having at least 99%, 95%, at least 90%, at least 85%, at least 80%, at least 70%, at least 60%, at least 50%, at least 40% or at least 25% amino acid identity or similarity to a polypeptide to a fragment comprising at least 5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, or 150 consecutive amino acids of a polypeptide whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 or by a homologous antisense nucleic acid. Identity or similarity may be determined using the FASTA version 3.0t78 algorithm with the default parameters. Alternatively, protein identity or similarity may be identified using BLASTP with the default parameters, BLASTX with the default parameters, or TBLASTN with the default parameters. (Altschul, S.F. et al. Gapped BLAST and PSI-BLAST: A New Generation of Protein Database Search Programs, Nucleic Acid Res. 25: 3389-3402 (1997). Additionally, homologous coding nucleic acids and the homologous polypeptides which they encode may be identified using a "reciprocal" best-hit analysis. To facilitate the identification of homologous coding nucleic acids and homologous polypeptides, paralogous genes within each of 51 organisms are identified and clustered prior to comparison to other organisms. Briefly, the polypeptide sequence of each polypeptide encoded by each open reading frame (ORF) in a given organism is compared to the polypeptide sequence encoded by every other ORF for that organism for each of the 51 pathogenic organisms (PathoSeq Sept 2001 release) using BLASTP 2.09 algorithm without filtering. Simultaneously, the polypeptide sequence encoded by each ORF of an organism is compared to the polypeptide sequences encoded by each of the ORFs in the remaining 51 organisms. Those polypeptides within a single organism that shared a higher degree of sequence identity to one another than to polypeptide sequences obtained from any other organisms are clustered as "paralog" sequences for "reciprocal" best-hit analysis.

For each reference organism, the 50 homologous coding nucleic acids (and the 50 homologous polypeptides which they encode) can be determined by identifying the ORFs in each of the 50 comparison organisms which encode a polypeptide sharing the highest degree of amino acid sequence identity to the polypeptide encoded by the ORF from the reference organism. The accuracy of the identification of the predicted homologous coding nucleic acids (and the homologous polypeptides which they encode) is confirmed by a "reciprocal" BLAST analysis in which the polypeptide sequence of the predicted homologous polypeptide is compared against the polypeptides encoded by each of the ORFS in the reference organism using BLASTP 2.09

algorithm without filtering. Only those polypeptides that share the highest degree of amino acid sequence identity in each portion of the two-way comparison are retained for further analysis.

The term homologous polypeptide also includes polypeptides having at least 99%, 95%, at least 90%, at least 85%, at least 80%, at least 70%, at least 60%, at least 50%, at least 40% or at least 25% amino acid identity or similarity to a polypeptide selected from the group consisting of SEQ ID NOs: 42,398-78,581 and polypeptides having at least 99%, 95%, at least 90%, at least 85%, at least 80%, at least 70%, at least 60%, at least 50%, at least 40% or at least 25% amino acid identity or similarity to a fragment comprising at least 5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, or 150 consecutive amino acids of a polypeptide selected from the group consisting of SEQ ID NOs: 42,398-78,581.

The invention also includes polynucleotides, preferably DNA molecules, that hybridize to one of the nucleic acids of SEQ ID NOs.: 1-6213, SEQ ID NOs.: 6214-42,397 or the complements of any of the preceding nucleic acids. Such hybridization may be under stringent or moderate conditions as defined above or under other conditions which permit specific hybridization. The nucleic acid molecules of the invention that hybridize to these DNA sequences include oligodeoxynucleotides ("oligos") which hybridize to the target gene under highly stringent or stringent conditions. In general, for oligos between 14 and 70 nucleotides in length the melting temperature (Tm) is calculated using the formula:

$$Tm\ (°C) = 81.5 + 16.6(\log[\text{monovalent cations (molar)}] + 0.41\ (\%\ G{+}C) - (500/N)$$

where N is the length of the probe. If the hybridization is carried out in a solution containing formamide, the melting temperature may be calculated using the equation:

$$Tm(°C) = 81.5 + 16.6(\log[\text{monovalent cations (molar)}] + 0.41(\%\ G{+}C) - (0.61)(\%\ \text{formamide}) - (500/N)$$

where N is the length of the probe. In general, hybridization is carried out at about 20-25 degrees below Tm (for DNA-DNA hybrids) or about 10-15 degrees below Tm (for RNA-DNA hybrids).

Other hybridization conditions are apparent to those of skill in the art (see, for example, Ausubel, F.M. *et al.*, eds., 1989, *Current Protocols in Molecular Biology*, Vol. I, Green Publishing Associates, Inc. and John Wiley & Sons, Inc., New York, at pp. 6.3.1-6.3.6 and 2.10.3.

The term, *Salmonella*, is the generic name for a large group of gram negative enteric bacteria that are closely related to *Escherichia coli*. The diseases caused by *Salmonella* are often due to contamination of foodstuffs or the water supply and affect millions of people each year. Traditional methods of *Salmonella* taxonomy were based on assigning a separate species name to each serologically distinguishable strain (Kauffmann, F 1966 The bacteriology of the *Enterobacteriaceae*. Munksgaard, Copenhagen). Serology of *Salmonella* is based on surface antigens (O [somatic] and H [flagellar]). Over 2,400 serotypes or serovars of *Salmonella* are known (Popoff, et al. 2000 Res. Microbiol. 151:63-65). Therefore, each serotype was considered to

be a separate species and often given names, accordingly (e.g. *S. paratyphi, S. typhimurium, S. typhi, S. enteriditis*, etc.).

However, by the 1970s and 1980s it was recognized that this system was not only cumbersome, but also inaccurate. Then, many *Salmonella* species were lumped into a single species (all serotypes and subgenera I, II, and IV and all serotypes of *Arizona*) with a second subspecies, *S. bongorii* also recognized (Crosa, et al., 1973, J. Bacteriol. 115:307-315). Though species designations are based on the highly variable surface antigens, the *Salmonella* are very similar otherwise with a major exception being pathogenicity determinants.

There has been some debate on the correct name for the *Salmonella* species. Currently (Brenner, et al. 2000 J. Clin. Microbiol. 38:2465-2467), the accepted name is *Salmonella enterica*. *S. enterica* is divided into six subspecies (I, *S. enterica* subsp. *enterica*; II, *S. enterica*, subsp. *salamae*; IIIa, *S. enterica* subsp. *arizonàe*; IIIb, *S. enterica* subsp. *diarizonae*; IV, *S. enterica* subsp. *houtenae*; and VI, *S. enterica* subsp. *indica*). Within subspecies I, serotypes are used to distinguish each of the serotypes or serovars (e.g. *S. enterica* serotype Enteriditis, *S. enterica* serotype Typhimurium, *S. enterica* serotype Typhi, and *S. enterica* serotype Choleraesuis, etc.). Current convention is to spell this out on first usage (*Salmonella enterica* ser. Typhimurium) and then use an abbreviated form (*Salmonella* Typhimurium or *S.* Typhimurium). Note, the genus and species names (*Salmonella enterica*) are italicized but not the serotype/serovar name (Typhimurium). Because the taxonomic committees have yet to officially approve of the actual species name, this latter system is what is employed by the CDC (Brenner, et al. 2000 J. Clin. Microbiol. 38:2465-2467). Due to the concerns of both taxonomic priority and medical importance, some of these serotypes might ultimately receive full species designations (*S.typhi* would be the most notable).

Therefore, as used herein "*Salmonella enterica* or *S. enterica*" includes serovars Typhi, Typhimurium, Paratyphi, Choleraesuis, etc." However, appeals of the "official" name are in process and the taxonomic designations may change (*S. choleraesuis* is the species name that could replace *S. enterica* based solely on priority).

By "identifying a compound" is meant to screen one or more compounds in a collection of compounds such as a combinatorial chemical library or other library of chemical compounds or to characterize a single compound by testing the compound in a given assay and determining whether it exhibits the desired activity.

By "inducer" is meant an agent or solution which, when placed in contact with a cell or microorganism, increases transcription, or inhibitor and/or promoter clearance/fidelity, from a desired promoter.

As used herein, "nucleic acid" means DNA, RNA, or modified nucleic acids. Thus, the terminology "the nucleic acid of SEQ ID NO: X" or "the nucleic acid comprising the nucleotide sequence" includes both the DNA sequence of SEQ ID NO: X and an RNA sequence in which the thymidines in the DNA sequence have been substituted with uridines in the RNA sequence and in which the deoxyribose backbone of the DNA sequence has been substituted with a ribose backbone

in the RNA sequence. Modified nucleic acids are nucleic acids having nucleotides or structures which do not occur in nature, such as nucleic acids in which the internucleotide phosphate residues with methylphosphonates, phosphorothioates, phosphoramidates, and phosphate esters. Nonphosphate internucleotide analogs such as siloxane bridges, carbonate brides, thioester bridges, as well as many others known in the art may also be used in modified nucleic acids. Modified nucleic acids may also comprise, α-anomeric nucleotide units and modified nucleotides such as 1,2-dideoxy-d-ribofuranose, 1,2-dideoxy-1-phenylribofuranose, and N^4, N^4-ethano-5-methyl-cytosine are contemplated for use in the present invention. Modified nucleic acids may also be peptide nucleic acids in which the entire deoxyribose-phosphate backbone has been exchanged with a chemically completely different, but structurally homologous, polyamide (peptide) backbone containing 2-aminoethyl glycine units.

As used herein, "sub-lethal" means a concentration of an agent below the concentration required to inhibit all cell growth.

Brief Description of the Drawings

Figure 1A illustrates a method for replacing a promoter using a promoter replacement cassette comprising a 5' region homologous to the sequence which is 5' of the natural promoter in the chromosome, the promoter which is to replace the chromosomal promoter and a 3' region which is homologous to sequences 3' of the natural promoter in the chromosome.

Figure 1B illustrates a method for replacing a promoter using a promoter replacement cassette comprising a nucleic acid encoding an identifiable or selectable marker disposed between the 5' region which is homologous to the sequence 5' of the natural promoter and the promoter which is to replace the chromosomal promoter and a transcriptional terminator 3' of the gene encoding an identifiable or selectable marker.

Figures 2A and 2B illustrate one method for identifying amplification products which are underrepresented or overrepresented in a culture.

Figures 3A and 3B illustrate another method for identifying amplification products which are underrepresented or overrepresented in a culture.

Figure 4 illustrates the results of a hybridization analysis where the antisense nucleic acid expressed by a strain in the culture is not complementary to all or a portion of the gene encoding the target of the compound (i.e. a nonspecific strain).

Figure 5 illustrates the results of a hybridization analysis where the antisense nucleic acid expressed by a strain in the culture is complementary to all or a portion of the gene encoding the target of the compound, the hybridization intensity for that strain will be intimately correlated with the concentration of the compound (i.e. a specific strain).

Figure 6 illustrates an oligonucleotide comprising a lac operator flanked on each side by 40 nucleotides homologous to the promoter is the promoter which drives expression of the *yabB yabC ftsL ftsI murE* genes in an operon for use in inserting the lac operator into the promoter.

Figure 7 is an IPTG dose response curve in *E. coli* transformed with an IPTG-inducible plasmid containing either an antisense clone to the *E. coli* ribosomal protein *rpl*W (AS-*rplW*) which is required for protein synthesis and essential for cell proliferation, or an antisense clone to the *elaD* (AS-*elaD*) gene which is not known to be involved in protein synthesis and which is also essential for proliferation.

Figure 8A is a tetracycline dose response curve in *E. coli* transformed with an IPTG-inducible plasmid containing antisense to *rplW* (AS-*rplW*) in the absence (0) or presence of IPTG at concentrations that result in 20% and 50% growth inhibition.

Figure 8B is a tetracycline dose response curve in *E. coli* transformed with an IPTG-inducible plasmid containing antisense to *elaD* (AS-*elaD*)in the absence (0) or presence of IPTG at concentrations that result in 20% and 50% growth inhibition.

Figure 9 is a graph showing the fold increase in tetracycline sensitivity of *E. coli* transfected with antisense clones to essential ribosomal proteins *L23* (AS-*rplW*) and *L7/L12* and *L10* (AS-*rplLrplJ*). Antisense clones to genes known to not be directly involved in protein synthesis, *atpB/E* (AS-*atpB/E*), *visC* (AS-*visC*), *elaD* (AS-*elaD*), *yohH* (AS-*yohH*), are much less sensitive to tetracycline.

Figure 10 illustrates the results of an assay in which *Staphylococcus aureus* cells transcribing an antisense nucleic acid complementary to the *gyrB* gene encoding the β subunit of gyrase were contacted with several antibiotics whose targets were known.

Figure 11 illustrates a microtitration plate which contains antibiotic and inducer at gradient concentrations in a matrix format in 10 times excess quantity.

Figure 12 illustrates the results of an experiment demonstrating that at appropriate concentrations of inducer, cells which overexpress the *defB* gene product were able to grow at elevated concentrations of the antibiotic actinonin

Figure 13 illustrates the results of an experiment demonstrating that at appropriate concentrations of inducer cells which overexpress the *folA* gene product were able to grow at elevated concentrations of the antibiotic trimethoprim.

Figure 14 illustrates the results of an experiment demonstrating that overexpression of the *fabI* gene confers resistance to triclosan, which acts on the gene product of the *fabI* gene, but does not confer resistance to cerulenin, trimethoprim, or actinonin, each of which act on other gene products.

Figure 15 illustrates the results of an experiment demonstrating that overexpression of the *folA* gene confers resistance to trimethoprim, which acts on the gene product of the *folA* gene but does not confer resistance to triclosan, cerulenin, or actinonin, each of which act on other gene products.

Figure 16 illustrates the results of an experiment demonstrating that overexpression of the *defB* gene conferred resistance to actinonin, which acts on the gene product of the *defB* gene but

does not confer resistance to cerulenin, trimethoprim, or triclosan, each of which act on other gene products.

Figure 17 illustrates the results of an experiment demonstrating that overexpression of the *fabF* gene conferred resistance to cerulenin, which acts on the gene product of the *fabF* gene, β keto-acyl carrier protein synthase but does not confer resistance to triclosan, trimethoprim, or actinonin, each of which act on other gene products.

Figure 18 illustrates the results of experiments in which a mixture of nine strains was grown wells in a 96 well plate in medium containing various concentrations of inducer and a sufficient concentration of actinonin, cerulenin, triclosan or trimethoprim to inhibit the growth of strains which do not overexpress the targets of these antibiotics.

Detailed Description of Embodiments of the Invention

The present invention describes a group of prokaryotic genes and gene families required for cellular proliferation. Exemplary genes and gene families from *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholera* and *Yersinia pestis* are provided. A proliferation-required gene or gene family is one where, in the absence or substantial reduction of a gene transcript and/or gene product, growth or viability of the cell or microorganism is reduced or eliminated. Thus, as used herein, the terminology "proliferation-required" or "required for proliferation" encompasses instances where the absence or substantial reduction of a gene transcript and/or gene product completely eliminates cell growth as well as instances where the absence of a gene transcript and/or gene product merely reduces cell growth. These proliferation-required genes can be used as potential targets for the generation of new antimicrobial agents. To achieve that goal, the present invention also encompasses assays for analyzing proliferation-required genes and for identifying compounds which interact with the gene and/or gene products of the proliferation-required genes. In addition, the present invention contemplates the expression of genes and the purification of the proteins encoded by the nucleic acid sequences identified as required proliferation genes and reported herein. The purified proteins can be

used to generate reagents and screen small molecule libraries or other candidate compound libraries for compounds that can be further developed to yield novel antimicrobial compounds.

The present invention also describes methods for identification of nucleotide sequences homologous to these genes and polypeptides described herein, including nucleic acids comprising nucleotide sequences homologous to the nucleic acids of SEQ ID NOS.: 6214-42397 and polypeptides homologous to the polypeptides of SEQ ID NOs.: 42398-78581. For example, these sequences may be used to identify homologous coding nucleic acids, homologous antisense nucleic acids, or homologous polypeptides in microorganisms such as *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* or any species falling within the genera of any of the above species. In some embodiments, the homologous coding nucleic acids, homologus antisense nucleic acids, or homologous polypeptides are identified in an organism other than *E. coli.*

The homologous coding nucleic acids, homologous antisense nucleic acids, or homologous polypeptides, may then be used in each of the methods described herein, including methods of identifying compounds which inhibit the proliferation of the organism containing the homologous coding nucleic acid, homologous antisense nucleic acid or homologous polypeptide, methods of inhibiting the growth of the organism containing the homologous coding nucleic acid, homologus antisense nucleic acid or homologous polypeptide, methods of identifying compounds which influence the activity or level of a gene product required for proliferation of the organism containing the homologous coding nucleic acid, homologous antisense nucleic acid or homologous

polypeptide, methods for identifying compounds or nucleic acids having the ability to reduce the level or activity of a gene product required for proliferation of the organism containing the homologous coding nucleic acid, homologous antisense nucleic acid or homologous polypeptide, methods of inhibiting the activity or expression of a gene in an operon required for proliferation of the organism containing the homologous coding nucleic acid, homologous antisense nucleic acid or homologous polypeptide, methods for identifying a gene required for proliferation of the organism containing the homologous coding nucleic acid, homologous antisense nucleic acid or homologous polypeptide, methods for identifying the biological pathway in which a gene or gene product required for proliferation of the organism containing the homologous coding nucleic acid, homologous antisense nucleic acid or homologous polypeptide lies, methods for identifying compounds having activity against biological pathway required for proliferation of the organism containing the homologous coding nucleic acid, homologous antisense nucleic acid or homologous polypeptide, methods for determining the biological pathway on which a test compound acts in the organism containing the homologous coding nucleic acid, homologous antisense nucleic acid or homologous polypeptide, methods of replacing an endogenous promoter with a regulatable promoter which controls the expression of the homologous coding nucleic acid, homologous antisense nucleic acid or homologous polypeptide, methods of inserting an operator within or near an endogenous promoter to provide regulatable expression of the homologous coding nucleic acid, homologous antisense nucleic acid or homologous polypeptide, methods of identifying the target on which a compound acts in the organism containing the homologous coding nucleic acid, homologous antisense nucleic acid or homologous polypeptide, and methods of inhibiting the proliferation of the organism containing the homologous coding nucleic acid, homologous antisense nucleic acid or homologous polypeptide in a subject. In some embodiments of the present invention, the methods are performed using an organism, other than *E. coli* or a gene or gene product from an organism other than *E. coli.*

One embodiment of the present invention utilizes a novel method to identify proliferation-required sequences. Generally, a library of nucleic acid sequences from a given source are subcloned or otherwise inserted immediately downstream of an inducible promoter on an appropriate vector, such as a *Staphylococcus aureus/E. coli* or *Pseudomonas aeruginosa/ E. coli* shuttle vector, or a vector which will replicate in both *Salmonella typhimurium* and *Klebsiella pneumoniae,* or other vector or shuttle vector capable of functioning in the intended organism, thus forming an expression library. It is generally preferred that expression is directed by a regulatable promoter sequence such that expression level can be adjusted by addition of variable concentrations of an inducer molecule or of an inhibitor molecule to the medium. For example, a number of regulatable promoters useful for regulating the expression of nucleic acid sequences over a wide range of expression levels are described in U.S. Patent Application Serial Number 10/032,393, filed December 21, 2001. Temperature activated promoters, such as promoters regulated by temperature sensitive repressors, such as the lambda C_{I857} repressor, are also envisioned. Although the insert nucleic acids may be derived from the chromosome

of the cell or microorganism into which the expression vector is to be introduced, because the insert is not in its natural chromosomal location, the insert nucleic acid is an exogenous nucleic acid for the purposes of the discussion herein. The term "expression" is defined as the production of a sense or antisense RNA molecule from a gene, gene fragment, genomic fragment, chromosome, operon or portion thereof. Expression can also be used to refer to the process of peptide or polypeptide synthesis. An expression vector is defined as a vehicle by which a ribonucleic acid (RNA) sequence is transcribed from a nucleic acid sequence carried within the expression vehicle. The expression vector can also contain features that permit translation of a protein product from the transcribed RNA message expressed from the exogenous nucleic acid sequence carried by the expression vector. Accordingly, an expression vector can produce an RNA molecule as its sole product or the expression vector can produce a RNA molecule that is ultimately translated into a protein product.

Once generated, the expression library containing the exogenous nucleic acid sequences is introduced into a population of cells (such as the organism from which the exogenous nucleic acid sequences were obtained) to search for genes that are required for bacterial proliferation. Because the library molecules are foreign, in context, to the population of cells, the expression vectors and the nucleic acid segments contained therein are considered exogenous nucleic acid.

Expression of the exogenous nucleic acid fragments in the test population of cells containing the expression library is then activated. Activation of the expression vectors consists of subjecting the cells containing the vectors to conditions that result in the expression of the exogenous nucleic acid sequences carried by the expression library. The test population of cells is then assayed to determine the effect of expressing the exogenous nucleic acid fragments on the test population of cells. Those expression vectors that negatively impact the growth of the cells upon induction of expression of the random sequences contained therein are identified, isolated, and purified for further study.

In some embodiments, vectors which comprises a regulatable fusion promoter selected from a suite of fusion promoters, wherein the promoter suite is useful for modulating both the basal and maximal levels of transcription of a nucleic acid over a wide dynamic range thus allowing the desired level of production of a transcript, can be used to express exogenous nucleic acids, including the nucleic acids of the present invention. Such promoters are described in U.S. Patent Application Serial Number 10/032,393, filed December 21, 2001, the disclosure of which is incorporated herein by reference in its entirety.

In some other embodiments, vectors useful for the production of stabilized mRNA having an increased lifetime (including antisense RNA) in Gram negative organisms are described in U.S. Provisional Patent Application Serial Number 60/343,512, filed December 21, 2001. Briefly, the stabilized antisense RNA may comprise an antisense RNA which was identified as inhibiting proliferation as described above which has been engineered to contain at least one stem loop flanking each end of the antisense nucleic acid. In some embodiments, the at least one stem-loop structure formed at the 5' end of the stabilized antisense nucleic acid comprises a flush, double stranded 5' end. In some embodiments, one or more of the stem loops comprises a rho independent

terminator. In additional embodiments, the stabilized antisense RNA lacks a ribosome binding site. In further embodiments, the stabilized RNA lacks sites which are cleaved by one or more RNAses, such as RNAse E or RNAse III. In some embodiments, the stabilized antisense RNA may be transcribed in a cell which the activity of at least one enzyme involved in RNA degradation has been reduced. For example, the activity of an enzyme such as RNase E, RNase II, RNase III, polynucleotide phosphorylase, and poly(A) polymerase, RNA helicase, enolase or an enzyme having similar functions may be reduced in the cell.

Alternatively, genes required for proliferation may be identified by replacing the natural promoter for the proliferation required gene with a regulatable promoter as described above. The growth of such strains under conditions in which the promoter is active or non-repressed is compared to the growth under conditions in which the promoter is inactive or repressed. If the strains fail to grow or grow at a substantially reduced rate under conditions in which the promoter is inactive or repressed but grow normally under conditions in which the promoter is active or non-repressed, then the gene which is operably linked to the regulatable promoter encodes a gene product required for proliferation. For example, proliferation-required genes and gene products identified using promoter replacement are described in U.S. Patent Application Serial Number 09/948,993.

For example, in some embodiments, the natural promoter may be replaced using techniques which employ homologous recombination to exchange a promoter present on the chromosome of the cell with the desired promoter. In such methodology, a nucleic acid comprising a promoter replacement cassette is introduced into the cell. As illustrated in Figure 1A, the promoter replacement cassette comprises a 5' region homologous to the sequence which is 5' of the natural promoter in the chromosome, the promoter which is to replace the chromosomal promoter and a 3' region which is homologous to sequences 3' of the natural promoter in the chromosome. In some embodiments, the promoter replacement cassette may also include a nucleic acid encoding an identifiable or selectable marker disposed between the 5' region which is homologous to the sequence 5' of the natural promoter and the promoter which is to replace the chromosomal promoter. If desired, the promoter replacement cassette may also contain a transcriptional terminator 3' of the gene encoding an identifiable or selectable marker, as illustrated in Figure 1B. As illustrated in Figure 1A and 1B, homologous recombination is allowed to occur between the chromosomal region containing the natural promoter and the promoter replacement cassette. Cells in which the promoter replacement cassette has integrated into the chromosome are identified or selected. To confirm that homologous recombination has occurred, the chromosomal structure of the cells may be verified by Southern analysis or PCR.

In some embodiments, the promoter replacement cassette may be introduced into the cell as a linear nucleic acid, such a PCR product or a restriction fragment. Alternatively, the promoter replacement may be introduced into the cell on a plasmid. Figures 1A and 1B illustrates the

replacement of a chromosomal promoter with a desired promoter through homologous recombination.

In some embodiments, the cell into which the promoter replacement cassette is introduced may carry mutations which enhance its ability to be transformed with linear DNA or which enhance the frequency of homologous recombination. For example, if the cell is an *Escherichia coli* cell it may have a mutation in the gene encoding Exonuclease V of the RecBCD recombination complex. If the cell is an *Escherichia coli* cell it may have a mutation that activates the RecET recombinase of the Rac prophage and/or a mutation that enhances recombination through the RecF pathway. For example, the *Escherichia coli* cells may be RecB or RecC mutants carrying an sbcA or sbcB mutation. Alternatively, the *Escherichia coli* cells may be recD mutants. In other embodiments the *Escherichia coli* cells may express the λ Red recombination genes. For example, *Escherichia coli* cells suitable for use in techniques employing homologous recombination have been described in Datsenko, K.A. and Wanner, B.L., PNAS 97:6640-6645 (2000); Murphy, K.C., J. Bact 180: 2053-2071 (1998); Zhang, Y., et al., Nature Genetics 20: 123-128 (1998); and Muyrers, J.P.P. et al., Genes & Development 14: 1971-1982 (2000). It will be appreciated that cells carrying mutations in similar genes may be constructed in organisms other than *Escherichia coli.*

In some embodiments of the present invention, a regulatable fusion promoter selected from a suite of fusion promoters, wherein the promoter suite is useful for modulating both the basal and maximal levels of transcription of a nucleic acid over a wide dynamic range thus allowing the desired level of production of a transcript, is with the promoter replacement methods described above. Such promoters are described in U.S. Patent Application Serial Number 10/032,393, filed December 21, 2001, the disclosure of which is incorported herein by reference in its entirety.

A variety of assays are contemplated to identify nucleic acid sequences that negatively impact growth upon expression. In one embodiment, growth in cultures expressing exogenous nucleic acid sequences and growth in cultures not expressing these sequences is compared. Growth measurements are assayed by examining the extent of growth by measuring optical densities. Alternatively, enzymatic assays can be used to measure bacterial growth rates to identify exogenous nucleic acid sequences of interest. Colony size, colony morphology, and cell morphology are additional factors used to evaluate growth of the host cells. Those cultures that fail to grow or grow at a reduced rate under expression conditions are identified as containing an expression vector encoding a nucleic acid fragment that negatively affects a proliferation-required gene.

Once exogenous nucleic acids of interest are identified, they are analyzed. The first step of the analysis is to acquire the nucleotide sequence of the nucleic acid fragment of interest. To achieve this end, the insert in those expression vectors identified as containing a nucleotide sequence of interest is sequenced, using standard techniques well known in the art. The next step of the process is to determine the source of the nucleotide sequence. As used herein "source" means the genomic region containing the cloned fragment.

Determination of the gene(s) corresponding to the nucleotide sequence is achieved by comparing the obtained sequence data with databases containing known protein and nucleotide sequences from various microorganisms. Thus, initial gene identification is made on the basis of significant sequence similarity or identity to either characterized or predicted *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa,* and *Salmonella typhimurium* genes or their encoded proteins and/or homologues in other species.

The number of nucleotide and protein sequences available in database systems has been growing exponentially for years. For example, the complete nucleotide sequences of *Caenorhabditis elegans* and several bacterial genomes, including *E. coli, Aeropyrum pernix, Aquifex aeolicus, Archaeoglobus fulgidus, Bacillus subtilis, Borrelia burgdorferi, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium tetani, Corynebacterium diptheria, Deinococcus radiodurans, Haemophilus influenzae, Helicobacter pylori 26695, Helicobacter pylori J99, Methanobacterium thermoautotrophicum, Methanococcus jannaschii, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Pseudomonas aeruginosa, Pyrococcus abyssi, Pyrococcus horikoshii, Rickettsia prowazekii, Synechocystis PCC6803, Thermotoga maritima, Treponema pallidum, Bordetella pertussis, Campylobacter jejuni, Clostridium acetobutylicum, Mycobacterium tuberculosis CSU#93, Neisseria gonorrhoeae, Neisseria meningitidis, Pseudomonas aeruginosa, Pyrobaculum aerophilum, Pyrococcus furiosus, Rhodobacter capsulatus, Salmonella typhimurium, Streptococcus mutans, Streptococcus pyogenes, Ureaplasma urealyticum* and *Vibrio cholera* are available. This nucleotide sequence information is stored in a number of databanks, such as GenBank, the National Center for Biotechnology Information (NCBI), the Genome Sequencing Center (http://genome.wustl.edu/gsc/salmonella.shtml), and the Sanger Centre (http://www.sanger.ac.uk/projects/S___typhi) which are publicly available for searching. A variety of computer programs are available to assist in the analysis of the sequences stored within these databases. FASTA, (W. R. Pearson (1990) "Rapid and Sensitive Sequence Comparison with FASTP and FASTA" Methods in Enzymology 183:63- 98), Sequence Retrieval System (SRS), (Etzold & Argos, SRS an indexing and retrieval tool for flat file data libraries. Comput. Appl. Biosci. 9:49-57, 1993) are two examples of computer programs that can be used to analyze sequences of interest. In one embodiment of the present invention, the BLAST family of computer programs, which includes BLASTN version 2.0 with the default parameters, or BLASTX version 2.0 with the default parameters, is used to analyze nucleotide sequences.

BLAST, an acronym for "Basic Local Alignment Search Tool," is a family of programs for database similarity searching. The BLAST family of programs includes: BLASTN, a nucleotide sequence database searching program, BLASTX, a protein database searching program where the input is a nucleic acid sequence; and BLASTP, a protein database searching program. BLAST programs embody a fast algorithm for sequence matching, rigorous statistical methods for judging the significance of matches, and various options for tailoring the program for special situations. Assistance

in using the program can be obtained by e-mail at blast@ncbi.nlm.nih.gov. tBLASTX can be used to translate a nucleotide sequence in all three potential reading frames into an amino acid sequence.

Bacterial genes are often transcribed in polycistronic groups. These groups comprise operons, which are a collection of genes and intergenic sequences under common regulation. The genes of an operon are transcribed on the same mRNA and are often related functionally. Given the nature of the screening protocol, it is possible that the identified exogenous nucleic acid corresponds to a gene or portion thereof with or without adjacent noncoding sequences, an intragenic sequence (i.e. a sequence within a gene), an intergenic sequence (i.e. a sequence between genes), a nucleotide sequence spanning at least a portion of two or more genes, a 5' noncoding region or a 3' noncoding region located upstream or downstream from the actual nucleotide sequence that is required for bacterial proliferation. Accordingly, it is often desirable to determine which gene(s) that is encoded within the operon is individually required for proliferation.

In one embodiment of the present invention, an operon is identified and then dissected to determine which gene or genes are required for proliferation. Operons can be identified by a variety of means known to those in the art. For example, the RegulonDB DataBase described by Huerta et al. (*Nucl. Acids Res.* 26:55-59, 1998), which may also be found on the website http://www.cifn.unam.mx/Computational_Biology/regulondb/, provides information about operons in *Escherichia coli*. The Subtilist database (http://bioweb.pasteur.fr/GenoList/SubtiList), (Moszer, I., Glaser, P. and Danchin, A. (1995) Microbiology 141: 261-268 and Moszer, I (1998) FEBS Letters 430: 28-36, may also be used to predict operons. This database lists genes from the fully sequenced, Gram positive bacteria, *Bacillus subtilis*, together with predicted promoters and terminator sites. This information can be used in conjunction with the *Staphylococcus aureus* genomic sequence data to predict operons and thus produce a list of the genes affected by the antisense nucleic acids of the present invention. The *Pseudomonas aeruginosa* web site (http://www.pseudomonas.com) can be used to help predict operon organization in this bacterium. The databases available from the Genome Sequencing Center (http://genome.wustl.edu/gsc/salmonella.shtml), and the Sanger Centre (http://www.sanger.ac.uk/projects/S___typhi) may be used to predict operons in *Salmonella typhimurium*. The TIGR microbial database has an incomplete version of the *E. faecalis* genome http://www.tigr.org/cgi-bin/BlastSearch/blast.cgi?organism=e_faecalis. One can take a nucleotide sequence and BLAST it for homologs.

A number of techniques that are well known in the art can be used to dissect the operon. Analysis of RNA transcripts by Northern blot or primer extension techniques are commonly used to analyze operon transcripts. In one aspect of this embodiment, gene disruption by homologous recombination is used to individually inactivate the genes of an operon that is thought to contain a gene required for proliferation.

Several gene disruption techniques have been described for the replacement of a functional gene with a mutated, non-functional (null) allele. These techniques generally involve the use of

homologous recombination. One technique using homologous recombination in *Staphylococcus aureus* is described in Xia et a.. 1999, Plasmid 42: 144-149. This technique uses crossover PCR to create a null allele with an in-frame deletion of the coding region of a target gene. The null allele is constructed in such a way that nucleotide sequences adjacent to the wild type gene are retained. These homologous sequences surrounding the deletion null allele provide targets for homologous recombination so that the wild type gene on the *Staphylococcus aureus* chromosome can be replaced by the constructed null allele. This method can be used with other bacteria as well, including *Salmonella* and *Klebsiella* species. Similar gene disruption methods that employ the counter selectable marker *sacB* (Schweizer, H. P., Klassen, T. and Hoang, T. (1996) Mol. Biol. of *Pseudomonas*. ASM press, 229-237, are available for *Pseudomonas, Salmonella* and *Klebsiella* species. *E. faecalis* genes can be disrupted by recombining in a non-replicating plasmid that contains an internal fragment to that gene (Leboeuf, C., L. Leblanc, Y. Auffray and A. Hartke. 2000. J. Bacteriol. 182:5799-5806.

The crossover PCR amplification product is subcloned into a suitable vector having a selectable marker, such as a drug resistance marker. In some embodiments the vector may have an origin of replication which is functional in *E. coli* or another organism distinct from the organism in which homologous recombination is to occur, allowing the plasmid to be grown in *E. coli* or the organism other than that in which homologous recombination is to occur, but may lack an origin of replication functional in *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae* or *Yersinia pestis* such that selection of the selectable marker requires integration of the vector into the homologous region of the *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus*

faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae or *Yersinia pestis* chromosome. Usually a single crossover event is responsible for this integration event such that the *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholera* or *Yersinia pestis* chromosome now contains a tandem duplication of the target gene consisting of one wild type allele and one deletion null allele separated by vector sequence. Subsequent resolution of the duplication results in both removal of the vector sequence and either restoration of the wild type gene or replacement by the in-frame deletion. The latter outcome will not occur if the gene should prove essential. A more detailed description of this method is provided in Example 10 below. It will be appreciated that this method may be practiced with any of the nucleic acids or organisms described herein.

Recombinant DNA techniques can be used to express the entire coding sequences of the gene identified as required for proliferation, or portions thereof. The over-expressed proteins can be used as reagents for further study. The identified exogenous sequences are isolated, purified, and cloned into a suitable expression vector using methods well known in the art. If desired, the nucleic acids can contain the nucleotide sequences encoding a signal peptide to facilitate secretion of the expressed protein.

Expression of fragments of the bacterial genes identified as required for proliferation is also contemplated by the present invention. The fragments of the identified genes can encode a polypeptide comprising at least 5, at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, at least 55, at least 60, at least 65, at least 75, or more than 75 consecutive amino

acids of a gene complementary to one of the identified sequences of the present invention. The nucleic acids inserted into the expression vectors can also contain endogenous sequences upstream and downstream of the coding sequence.

When expressing the encoded protein of the identified nucleic acid required for bacterial proliferation or a fragment thereof, the nucleic acid to be expressed is operably linked to a promoter in an expression vector using conventional cloning technology. The expression vector can be any of the bacterial, insect, yeast, or mammalian expression systems known in the art. Commercially available vectors and expression systems are available from a variety of suppliers including Genetics Institute (Cambridge, MA), Stratagene (La Jolla, California), Promega (Madison, Wisconsin), and Invitrogen (San Diego, California). If desired, to enhance expression and facilitate proper protein folding, the codon usage and codon bias of the sequence can be optimized for the particular expression organism in which the expression vector is introduced, as explained by Hatfield, et al., U.S. Patent No. 5,082,767, incorporated herein by this reference. Fusion protein expression systems are also contemplated by the present invention.

Following expression of the protein encoded by the identified exogenous nucleic acid, the protein may be purified. Protein purification techniques are well known in the art. Proteins encoded and expressed from identified exogenous nucleic acids can be partially purified using precipitation techniques, such as precipitation with polyethylene glycol. Alternatively, epitope tagging of the protein can be used to allow simple one step purification of the protein. In addition, chromatographic methods such as ion-exchange chromatography, gel filtration, use of hydroxyapaptite columns, immobilized reactive dyes, chromatofocusing, and use of high-performance liquid chromatography, may also be used to purify the protein. Electrophoretic methods such as one-dimensional gel electrophoresis, high-resolution two-dimensional polyacrylamide electrophoresis, isoelectric focusing, and others are contemplated as purification methods. Also, affinity chromatographic methods, comprising antibody columns, ligand presenting columns and other affinity chromatographic matrices are contemplated as purification methods in the present invention.

The purified proteins produced from the gene encoding sequences identified as required for proliferation can be used in a variety of protocols to generate useful antimicrobial reagents. In one embodiment of the present invention, antibodies are generated against the proteins expressed from the identified exogenous nucleic acids. Both monoclonal and polyclonal antibodies can be generated against the expressed proteins. Methods for generating monoclonal and polyclonal antibodies are well known in the art. Also, antibody fragment preparations prepared from the produced antibodies discussed above are contemplated.

In addition, the purified protein, fragments thereof, or derivatives thereof may be administered to an individual in a pharmaceutically acceptable carrier to induce an immune response against the protein. Preferably, the immune response is a protective immune response which protects the individual. Methods for determining appropriate dosages of the protein and pharmaceutically acceptable carriers may be determined empiracally and are familiar to those skilled in the art.

Another application for the purified proteins of the present invention is to screen small molecule libraries for candidate compounds active against the various target proteins of the present invention. Advances in the field of combinatorial chemistry provide methods, well known in the art, to produce large numbers of candidate compounds that can have a binding, or otherwise inhibitory effect on a target protein. Accordingly, the screening of small molecule libraries for compounds with binding affinity or inhibitory activity for a target protein produced from an identified gene is contemplated by the present invention.

In some embodiments of the present invention, a cell sensitized by expressing an an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, an antisense nucleic acid comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a nucleic acid complementary to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, a nucleic acid complementary to a nucleic acid comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, a nucleic acid complementary to a nucleic acid which encodes a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581, a nucleic acid complementary to a nucleic acid which encodes at least 5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, or 150 consecutive amino acids of a polypeptide sequence selected from the group consisting of SEQ ID NOs.: 42398-78581, a homologous antisense nucleic acid, an antisense nucleic acid comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of a homologous nucleic acid, a nucleic acid complementary to a homologous coding nucleic acid, a nucleic acid complementary to at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of a homologous coding nucleic acid, a nucleic acid complementary to a nucleic acid which encodes a homologous polypeptide, or a nucleic acid complementary to a nucleic acid which encodes at least 5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, or 150 consecutive amino acids of a homologous polypeptide, is contacted with one or more candidate compounds from a small molecule library. Candidate compounds which further inhibit the proliferation of the sensitized cell may be identified as possessing inhibitory activity for a target protein or product produced by the gene to which the antisense sequence is complementary.

A number of vectors useful in the above methods are described in U.S. Patent Application Serial Number 10/032,393, filed December 21, 2001.

In some embodiments of the present invention, the methods for the production of stabilized RNA, as described in U.S. Patent Application Serial Number 60/343,512, can be used for the production of a stabilized transcript, which corresponds to a nucleic acid described herein, having an increased lifetime in Gram-negative organisms. Briefly, the stabilized antisense RNA may comprise an antisense RNA which was identified as inhibiting proliferation as described above

which has been engineered to contain at least one stem loop flanking each end of the antisense nucleic acid. In some embodiments, the at least one stem-loop structure formed at the 5' end of the stabilized antisense nucleic acid comprises a flush, double stranded 5' end. In some embodiments, one or more of the stem loops comprises a rho independent terminator. In additional embodiments, the stabilized antisense RNA lacks a ribosome binding site. In further embodiments, the stabilized RNA lacks sites which are cleaved by one or more RNAses, such as RNAse E or RNAse III. In some embodiments, the stabilized antisense RNA may be transcribed in a cell which the activity of at least one enzyme involved in RNA degradation has been reduced. For example, the activity of an enzyme such as RNase E, RNase II, RNase III, polynucleotide phosphorylase, and poly(A) polymerase, RNA helicase, enolase or an enzyme having similar functions may be reduced in the cell.

The present invention further contemplates utility against a variety of other pathogenic microorganisms in addition to *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae* and *Yersinia pestis*. For example, homologous coding nucleic acids, homologous antisense nucleic acids or homologous polypeptides from other pathogenic microorganisms (including nucleic acids homologous to the nucleic acids of SEQ ID NOs.: 6214-42397, nucleic acids homologous to the antisense nucleic acids of SEQ ID NOs.: 1-6213, and polypeptides homologous to the polypeptides of SEQ ID NOs.: 42398-78581) may be identified using methods such as those described herein. The homologous coding nucleic acids, homologous antisense nucleic acids or homologous polypeptides may be used to identify compounds which inhibit the proliferation of these other pathogenic microorganisms using methods such as those described herein.

For example, the proliferation-required nucleic acids, antisense nucleic acids, and polypeptides from *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia*

pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae or *Yersinia pestis* described herein (including the nucleic acids of SEQ ID NOs.: 6214-42397, the antisense nucleic acids of SEQ ID NOs: 1-6213, and the polypeptides of SEQ ID NOs.: 42398-78581) may be used to identify homologous coding nucleic acids, homologous antisense nucleic acids or homologous polypeptides required for proliferation in prokaryotes and eukaryotes. For example, nucleic acids or polypeptides required for the proliferation of protists, such as *Plasmodium* spp.; plants; animals, such as *Entamoeba* spp. *and Contracaecum* spp; and fungi including *Candida* spp., (e.g., *Candida albicans*), *Cryptococcus neoformans*, and *Aspergillus fumigatus* may be identified. In one embodiment of the present invention, monera, specifically bacteria, including both Gram positive and Gram negative bacteria, are probed in search of novel gene sequences required for proliferation. Likewise, homologous antisense nucleic acids which may be used to inhibit growth of these organisms or to identify antibiotics may also be identified. These embodiments are particularly important given the rise of drug resistant bacteria.

The number of bacterial species that are becoming resistant to existing antibiotics is growing. A partial list of these microorganisms includes: *Escherichia* spp., such as *E. coli*, *Enterococcus* spp, such as *E. faecalis*; *Pseudomonas* spp., *such as P. aeruginosa*, *Clostridium* spp., such as *C. botulinum*, *Haemophilus* spp., such as *H. influenzae*, *Enterobacter* spp., such as *E. cloacae*, *Vibrio* spp., such as *V. cholera; Moraxala* spp., such as *M. catarrhalis*; *Streptococcus* spp., such as *S. pneumoniae*, *Neisseria* spp., such as *N. gonorrhoeae; Mycoplasma* spp., such as *Mycoplasma pneumoniae; Salmonella typhimurium*; *Helicobacter pylori*; *Escherichia coli;* and *Mycobacterium tuberculosis*. The genes and polypeptides identified as required for the proliferation of *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella*

multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae or *Yersinia pestis* (including the nucleic acids of SEQ ID NOs.: 6214-42397, the sequences complementary to the nucleic acids of SEQ ID NOs.: 6214-42397, and the polypeptides of SEQ ID NOs.: 42398-78581) can be used to identify homologous coding nucleic acids or homologous polypeptides required for proliferation from these and other organisms using methods such as nucleic acid hybridization and computer database analysis. Likewise, the antisense nucleic acids which inhibit proliferation of *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae* or *Yersinia pestis* (including the antisense nucleic acids of SEQ ID NOs.: 1-6213 or the sequences complementary thereto) may also be used to identify antisense nucleic acids which inhibit proliferation of these and other microorganisms or cells using nucleic acid hybridization or computer database analysis.

In one embodiment of the present invention, the nucleic acid sequences from *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma*

urealyticum, *Vibrio cholerae* or *Yersinia pestis* (including the nucleic acids of SEQ ID NOs.: 6214-42397 and the antisense nucleic acids of SEQ ID NOs. 1-6213) are used to screen genomic libraries generated from *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Yersinia pestis* and other bacterial species of interest. For example, the genomic library may be from Gram positive bacteria, Gram negative bacteria or other organisms including *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* or any species falling within the genera of any of the above species, including coagulase negative species of *Staphylococcus*. In some embodiments, the genomic

library may be from an organism other than *E. coli*. Standard molecular biology techniques are used to generate genomic libraries from various cells or microorganisms. In one aspect, the libraries are generated and bound to nitrocellulose paper. The identified exogenous nucleic acid sequences of the present invention can then be used as probes to screen the libraries for homologous sequences.

For example, the libraries may be screened to identify homologous coding nucleic acids or homologous antisense nucleic acids comprising nucleotide sequences which hybridize under stringent conditions to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213, nucleic acids comprising nucleotide sequences which hybridize under stringent conditions to a fragment comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of one of SEQ ID NOs. 1-6213, nucleic acids comprising nucleotide sequences which hybridize under stringent conditions to a nucleic acid complementary to one of SEQ ID NOs. 1-6213, nucleic acids comprising nucleotide sequences which hybridize under stringent conditions to a fragment comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of the sequence complementary to one of SEQ ID NOs. 1-6213, nucleic acids comprising nucleotide sequences which hybridize under stringent conditions to a nucleic acid selected from the group consisting of SEQ ID NOS.: 6214-42397, nucleic acids comprising nucleotide sequences which hybridize under stringent conditions to a fragment comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of one of SEQ ID NOS.: 6214-42397, nucleic acids comprising nucleotide sequences which hybridize under stringent conditions to a nucleic acid complementary to one of SEQ ID NOS.: 6214-42397, nucleic acids comprising nucleotide sequences which hybridize under stringent conditions to a fragment comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of the sequence complementary to one of SEQ ID NOS.: 6214-42397.

The libraries may also be screened to identify homologous nucleic coding nucleic acids or homologous antisense nucleic acids comprising nucleotide sequences which hybridize under moderate conditions to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213, nucleic acids comprising nucleotide sequences which hybridize under moderate conditions to a fragment comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of one of SEQ ID NOs. 1-6213, nucleic acids comprising nucleotide sequences which hybridize under moderate conditions to a nucleic acid complementary to one of SEQ ID NOs. 1-6213, nucleic acids comprising nucleotide sequences which hybridize under moderate conditions to a fragment comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of the sequence complementary to one of SEQ ID NOs. 1-6213, nucleic acids comprising nucleotide sequences which hybridize under moderate conditions to a nucleic acid selected from the group consisting of SEQ ID NOS.: 6214-42397, nucleic acids comprising nucleic acid sequences which hybridize under moderate conditions to a fragment comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500

consecutive nucleotides of one of SEQ ID NOS.: 6214-42397, nucleic acids comprising nucleotide sequences which hybridize under moderate conditions to a nucleic acid complementary to one of SEQ ID NOS.: 6214-42397 and nucleic acids comprising nucleotide sequences which hybridize under moderate conditions to a fragment comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of the sequence complementary to one of SEQ ID NOS.: 6214-42397.

The homologous coding nucleic acids, homologous antisense nucleic acids or homologous polypeptides identified as above can then be used as targets or tools for the identification of new, antimicrobial compounds using methods such as those described herein. In some embodiments, the homologous coding nucleic acids, homologous antisense nucleic acids, or homologous polypeptides may be used to identify compounds with activity against more than one microorganism. [Placeholder]

For example, the preceding methods may be used to isolate homologous coding nucleic acids or homologous antisense nucleic acids comprising a nucleotide sequence with at least 97%, at least 95%, at least 90%, at least 85%, at least 80%, or at least 70% nucleotide sequence identity to a nucleotide sequence selected from the group consisting of one of the sequences of SEQ ID NOS. 1-6213, fragments comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides thereof, and the sequences complementary thereto. The preceding methods may also be used to isolate homologous coding nucleic acids or homologous antisense nucleic acids comprising a nucleotide sequence with at least 97%, at least 95%, at least 90%, at least 85%, at least 80%, or at least 70% nucleotide sequence identity to a nucleotide sequence selected from the group consisting of one of the nucleotide sequences of SEQ ID NOS.: 6214-42397, fragments comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides thereof, and the sequences complementary thereto. Identity may be measured using BLASTN version 2.0 with the default parameters. (Altschul, S.F. et al. Gapped BLAST and PSI-BLAST: A New Generation of Protein Database Search Programs, Nucleic Acid Res. 25: 3389-3402 (1997). For example, the homologous polynucleotides may comprise a coding sequence which is a naturally occurring allelic variant of one of the coding sequences described herein. Such allelic variants may have a substitution, deletion or addition of one or more nucleotides when compared to the nucleic acids of SEQ ID NOs: 1-6213, SEQ ID NOS.: 6214-42397 or the nucleotide sequences complementary thereto.

Additionally, the above procedures may be used to isolate homologous coding nucleic acids which encode polypeptides having at least 99%, 95%, at least 90%, at least 85%, at least 80%, at least 70%, at least 60%, at least 50%, at least 40% or at least 25% amino acid identity or similarity to a polypeptide comprising the sequence of one of SEQ ID NOs: 42398-78581 or to a polypeptpide whose expression is inhibited by a nucleic acid of one of SEQ ID NOs: 1-6213 or fragments comprising at least 5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, or 150 consecutive amino acids thereof as determined using the FASTA version 3.0t78 algorithm with the default parameters. Alternatively, protein identity or similarity may be identified using BLASTP with the default

parameters, BLASTX with the default parameters, or TBLASTN with the default parameters. (Altschul, S.F. et al. Gapped BLAST and PSI-BLAST: A New Generation of Protein Database Search Programs, Nucleic Acid Res. 25: 3389-3402 (1997).

Alternatively, homologous coding nucleic acids, homologous antisense nucleic acids or homologous polypeptides may be identified by searching a database to identify sequences having a desired level of nucleotide or amino acid sequence homology to a nucleic acid or polypeptide involved in proliferation or an antisense nucleic acid to a nucleic acid involved in microbial proliferation. A variety of such databases are available to those skilled in the art, including GenBank and GenSeq. In some embodiments, the databases are screened to identify nucleic acids with at least 97%, at least 95%, at least 90%, at least 85%, at least 80%, or at least 70% nucleotide sequence identity to a nucleic acid required for proliferation, an antisense nucleic acid which inhibits proliferation, or a portion of a nucleic acid required for proliferation or a portion of an antisense nucleic acid which inhibits proliferation. For example, homologous coding sequences may be identified by using a database to identify nucleic acids homologous to one of SEQ ID Nos. 1-6213, homologous to fragments comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides thereof, nucleic acids homologous to one of SEQ ID NOS.: 6214-42397, homologous to fragments comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of one of SEQ ID NOS.: 6214-42397, nucleic acids homologous to one of SEQ ID Nos. 1-6213, homologous to fragments comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides thereof or nucleic acids homologous to the sequences complementary to any of the preceding nucleic acids. In other embodiments, the databases are screened to identify polypeptides having at least 99%, 95%, at least 90%, at least 85%, at least 80%, at least 70%, at least 60%, at least 50%, at least 40% or at least 25% amino acid sequence identity or similarity to a polypeptide involved in proliferation or a portion thereof. For example, the database may be screened to identify polypeptides homologous to a polypeptide comprising one of SEQ ID NOs: 42398-78581, a polypeptide whose expression is inhibited by a nucleic acid of one of SEQ ID NOs: 1-6213 or homologous to fragments comprising at least 5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, or 150 consecutive amino acids of any of the preceding polypeptides. In some embodiments, the database may be screened to identify homologous coding nucleic acids, homologous antisense nucleic acids or homologous polypeptides from cells or microorganisms other than the *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis,*

Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae or *Yersinia pestis* species from which they were obtained. For example the database may be screened to identify homologous coding nucleic acids, homologous antisense nucleic acids or homologous polypeptides from microorganisms such as *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* or any species falling within the genera of any of the above species, including coagulase negative *Staphylococcus* . In some embodiments, the homologous coding nucleic acids, homologous antisense nucleic acids, or homologous polypeptides are from an organism other than *E. coli*.

In another embodiment, gene expression arrays and microarrays can be employed. Gene expression arrays are high density arrays of DNA samples deposited at specific locations on a glass chip, nylon membrane, or the like. Such arrays can be used by researchers to quantify relative gene expression under different conditions. Gene expression arrays are used by researchers to help identify optimal drug targets, profile new compounds, and determine disease pathways. An example of this technology is found in U.S. Patent No. 5,807,522.

It is possible to study the expression of all genes in the genome of a particular microbial organism using a single array. For example, the arrays may consist of 12 x 24 cm nylon filters containing PCR products corresponding to ORFs from *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae* or *Yersinia pestis* (including the nucleic acids of SEQ ID NOs.: 6214-42397) . 10 ngs of each PCR product are spotted every 1.5 mm on the filter. Single stranded labeled cDNAs are prepared for hybridization to the array (no second strand synthesis or amplification step is done) and placed in contact with the filter. Thus the labeled cDNAs are of "antisense" orientation. Quantitative analysis is done by phosphorimager.

Hybridization of cDNA made from a sample of total cell mRNA to such an array followed by detection of binding by one or more of various techniques known to those in the art results in a signal at each location on the array to which cDNA hybridized. The intensity of the hybridization signal obtained at each location in the array thus reflects the amount of mRNA for that specific gene that was present in the sample. Comparing the results obtained for mRNA isolated from cells grown under different conditions thus allows for a comparison of the relative amount of expression of each individual gene during growth under the different conditions.

Gene expression arrays may be used to analyze the total mRNA expression pattern at various time points after induction of an antisense nucleic acid complementary to a proliferation-required gene. Analysis of the expression pattern indicated by hybridization to the array provides information on other genes whose expression is influenced by antisense expression. For example, if the antisense is complementary to a gene for ribosomal protein L7/L12 in the 50S subunit, levels of other mRNAs may be observed to increase, decrease or stay the same following expression of antisense to the L7/L12 gene. If the antisense is complementary to a different 50S subunit ribosomal protein mRNA (e.g. L25), a different mRNA expression pattern may result. Thus, the mRNA expression pattern observed following expression of an antisense nucleic acid comprising a nucleotide sequence complementary to a proliferation required gene may identify other proliferation-required nucleic acids. In addition, the mRNA expression patterns observed when the

bacteria are exposed to candidate drug compounds or known antibiotics may be compared to those observed with antisense nucleic acids comprising a nucleotide sequence complementary to a proliferation-required nucleic acid. If the mRNA expression pattern observed with the candidate drug compound is similar to that observed with the antisense nucleic acid, the drug compound may be a promising therapeutic candidate. Thus, the assay would be useful in assisting in the selection of promising candidate drug compounds for use in drug development.

In cases where the source of nucleic acid deposited on the array and the source of the nucleic acid being hybridized to the array are from two different cells or microorganisms, gene expression arrays can identify homologous nucleic acids in the two cells or microorganisms.

The present invention also contemplates additional methods for screening other microorganisms for proliferation-required genes. In one aspect of this embodiment, an antisense nucleic acid comprising a nucleotide sequence complementary to the proliferation-required sequences from *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae* or *Yersinia pestis*, or a portion thereof, is transcribed in an antisense orientation in such a way as to alter the level or activity of a nucleic acid required for proliferation of an autologous or heterologous cell or microorganism. For example, the antisense nucleic acid may be a homologous antisense nucleic acid such as an antisense nucleic acid homologous to the nucleotide sequence complementary to one of SEQ ID NOs.: 6214-42397, an antisense nucleic acid comprising a nucleotide sequence homologous to one of SEQ ID Nos.: 1-6213, or an antisense nucleic acid comprising a nucleotide sequence complementary to a portion of any of the preceding nucleic acids. The cell or microorganism transcribing the homologous antisense nucleic acid may be used in a cell-based assay, such as those described herein, to identify candidate antibiotic compounds. In another embodiment, the conserved portions of nucleotide sequences identified as proliferation-required can be used to generate degenerate primers for use in the polymerase chain reaction (PCR). The PCR technique is well known in the art. The successful production of a PCR product using degenerate primers generated from the nucleotide sequences identified herein indicates the presence of a homologous gene sequence in the species being screened.

This homologous gene is then isolated, expressed, and used as a target for candidate antibiotic compounds. In another aspect of this embodiment, the homologous gene (for example a homologous coding nucleic acid) thus identified, or a portion thereof, is transcribed in an autologous cell or microorganism or in a heterologous cell or microorganism in an antisense orientation in such a way as to alter the level or activity of a homologous gene required for proliferation in the autologous or heterologous cell or microorganism. Alternatively, a homologous antisense nucleic acid may be transcribed in an autologous or heterologous cell or microorganism in such a way as to alter the level or activity of a gene product required for proliferation in the autologous or heterologous cell or microorganism.

The nucleic acids homologous to the genes required for the proliferation of *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae* or *Yersinia pestis* or the sequences complementary thereto may be used to identify homologous coding nucleic acids or homologous antisense nucleic acids from cells or microorganisms other than *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae* or *Yersinia pestis* to inhibit the proliferation of cells or microorganisms other than

Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae or *Yersinia pestis* by inhibiting the activity or reducing the amount of the identified homologous coding nucleic acid or homologous polypeptide in the cell or microorganism other than *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae* or *Yersinia pestis* or to identify compounds which inhibit the growth of cells or microorganisms other than *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus*

mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae or *Yersinia pestis* as described below. For example, the nucleic acids homologous to proliferation-required genes from *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae* or *Yersinia pestis* or the sequences complementary thereto may be used to identify compounds which inhibit the growth of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica,*

Yersinia pestis or any species falling within the genera of any of the above species. In some embodiments of the present invention, the nucleic acids homologous to proliferation-required sequences from *Escherichia coli*, *Staphylococcus aureus*, *Enterococcus faecalis*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Acinetobacter baumannii*, *Bacillus anthracis*, *Bacteroides fragilis*, *Bordetella pertussis*, *Borrelia burgdorferi*, *Burkholderia cepacia*, *Burkholderia fungorum*, *Burkholderia mallei*, *Campylobacter jejuni*, *Chlamydia pneumoniae*, *Chlamydia trachomatis*, *Clostridium acetobutylicum*, *Clostridium botulinum*, *Clostridium difficile*, *Corynebacterium diptheriae*, *Enterobacter cloacae*, *Enterococcus faecium*, *Haemophilus influenzae*, *Helicobacter pylori*, *Legionella pneumophila*, *Listeria monocytogenes*, *Moraxella catarrhalis*, *Mycobacterium avium*, *Mycobacterium bovis*, *Mycobacterium leprae*, *Mycobacterium tuberculosis*, *Mycoplasma genitalium*, *Mycoplasma pneumoniae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Pasteurella multocida*, *Proteus mirabilis*, *Pseudomonas putida*, *Pseudomonas syringae*, *Salmonella paratyphi*, *Salmonella typhi*, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *Streptococcus mutans*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Treponema pallidum*, *Ureaplasma urealyticum*, *Vibrio cholerae* or *Yersinia pestis* (including nucleic acids homologous to one of SEQ ID NOs.: 6214-42397) or the sequences complementary thereto (including nucleic acids homologous to one of SEQ ID NOs.: 1-6213) are used to identify proliferation-required sequences in an organism other than *E. coli*.

In another embodiment of the present invention, antisense nucleic acids complementary to the sequences identified as required for proliferation or portions thereof (including antisense nucleic acids comprising a nucleotide sequence complementary to one of SEQ ID NOs.: 6214-42397 or portions thereof, such as the nucleic acids of SEQ ID NOs.: 1-6213) are transferred to vectors capable of function within a species other than the species from which the sequences were obtained. For example, the vector may be functional in *Acinetobacter baumannii*, *Anaplasma marginale*, *Aspergillus fumigatus*, *Bacillus anthracis*, *Bacteroides fragilis*, *Bordetella pertussis*, *Borrelia burgdorferi*, *Burkholderia cepacia*, *Burkholderia fungorum*, *Burkholderia mallei*, *Campylobacter jejuni*, *Candida albicans*, *Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis*, *Candida parapsilosis*, *Candida guilliermondii*, *Candida krusei*, *Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis*, *Chlamydia pneumoniae*, *Chlamydia trachomatis*, *Clostridium acetobutylicum*, *Clostridium botulinum*, *Clostridium difficile*, *Clostridium perfringens*, *Coccidioides immitis*, *Corynebacterium diptheriae*, *Cryptococcus neoformans*, *Enterobacter cloacae*, *Enterococcus faecalis*, *Enterococcus faecium*, *Escherichia coli*, *Haemophilus influenzae*, *Helicobacter pylori*, *Histoplasma capsulatum*, *Klebsiella pneumoniae*, *Legionella pneumophila*, *Listeria monocytogenes*, *Moraxella catarrhalis*, *Mycobacterium avium*, *Mycobacterium bovis*, *Mycobacterium leprae*, *Mycobacterium tuberculosis*, *Mycoplasma genitalium*, *Mycoplasma pneumoniae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Nocardia asteroides*, *Pasteurella haemolytica*, *Pasteurella multocida*, *Pneumocystis carinii*, *Proteus mirabilis*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Pseudomonas putida*, *Pseudomonas syringae*, *Salmonella bongori*,

Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis or any species falling within the genera of any of the above species. In some embodiments of the present invention, the vector may be functional in an organism other than *E. coli*. As would be appreciated by one of ordinary skill in the art, vectors may contain certain elements that are species specific. These elements can include promoter sequences, operator sequences, repressor genes, origins of replication, ribosomal binding sequences, termination sequences, and others. To use the antisense nucleic acids, one of ordinary skill in the art would know to use standard molecular biology techniques to isolate vectors containing the sequences of interest from cultured bacterial cells, isolate and purify those sequences, and subclone those sequences into a vector adapted for use in the species of bacteria to be screened.

Vectors for a variety of other species are known in the art. For example, numerous vectors which function in *E. coli* are known in the art. Also, Pla et al. have reported an expression vector that is functional in a number of relevant hosts including: *Salmonella typhimurium, Pseudomonas putida, and Pseudomonas aeruginosa*. *J. Bacteriol.* 172(8):4448-55 (1990). Brunschwig and Darzins (Gene (1992) 111:35-4, described a shuttle expression vector for *Pseudomonas aeruginosa*. Vectors useful for the production of stabilized mRNA having an increased lifetime (including antisense RNA) in Gram negative organisms are described in U.S. Provisional Patent Application Serial Number 60/343,512, filed December 21, 2001. Similarly many examples exist of expression vectors that are freely transferable among various Gram positive microorganisms. Expression vectors for *Enterococcus faecalis* may be engineered by incorporating suitable promoters into a pAK80 backbone (Israelsen, H., S. M. Madsen, A. Vrang, E. B. Hansen and E. Johansen. 1995. *Appl. Environ. Microbiol.* 61:2540-2547. A number of vectors useful for nucleic acid expression (including antisense nucleic acid expression) in *Enterococcus faecalis, Staphylococcus areus* as well as other Gram positive organisms are described in U.S. Patent Application Serial Number 10/032,393, filed December 21, 2001.

Following the subcloning of the antisense nucleic acids complementary to proliferation-required sequences from *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis,*

Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae or *Yersinia pestis* or portions thereof into a vector functional in a second cell or microorganism of interest (i.e. a cell or microorganism other than the one from which the identified nucleic acids were obtained), the antisense nucleic acids are conditionally transcribed to test for bacterial growth inhibition. The nucleotide sequences of the nucleic acids from *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae* or *Yersinia pestis* that, when transcribed, inhibit growth of the second cell or microorganism are compared to the known genomic sequence of the second cell or microorganism to identify the homologous gene from the second organism. If the homologous sequence from the second cell or microorganism is not known, it may be identified and isolated by hybridization to the proliferation-required *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio*

cholerae or *Yersinia pestis* sequence of interest or by amplification using PCR primers based on the proliferation-required nucleotide sequence of interest as described above. In this way, sequences which may be required for the proliferation of the second cell or microorganism may be identified. For example, the second microorganism may be *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* or any species falling within the genera of any of the above species. In some embodiments of the present invention, the second microorganism is an organism other than E. coli.

The homologous nucleic acid sequences from the second cell or microorganism which are identified as described above may then be operably linked to a promoter, such as an inducible promoter, in an antisense orientation and introduced into the second cell or microorganism. The techniques described herein for identifying *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus*

mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae or *Yersinia pestis* genes required for proliferation may thus be employed to determine whether the identified nucleotide sequences from a second cell or microorganism inhibit the proliferation of the second cell or microorganism. For example, the second microorganism may be *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* or any species falling within the genera of any of the above species. In some embodiments of the present invention, the second microorganism may be an organism other than E. coli.

Antisense nucleic acids required for the proliferation of microorganisms other than *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium*

tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae or *Yersinia pestis* or the genes corresponding thereto, may also be hybridized to a microarray containing the *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae* or *Yersinia pestis* (including the nucleic acids of SEQ ID NOs.: 6214-42397) to gauge the homology between the *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae* or *Yersinia pestis* sequences and the proliferation-required nucleic acids from other cells or microorganisms. For example, the proliferation-required nucleic acid may be from *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida*

guilliermondii, Candida krusei, Candida kefyr (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* or any species falling within the genera of any of the above species. In some embodiments of the present invention, the proliferation-required nucleotide sequences from *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae* or *Yersinia pestis* or homologous nucleic acids are used to identify proliferation-required sequences in an organism other than E. coli. In some embodiments of the present invention, the proliferation-required sequences may be from an organism other than E. coli. The proliferation-required nucleic acids from a cell or microorganism other than *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae,*

Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae or *Yersinia pestis* may be hybridized to the array under a variety of conditions which permit hybridization to occur when the probe has different levels of homology to the nucleotide sequence on the microarray. This would provide an indication of homology across the cells or microorganisms as well as clues to other possible essential genes in these cells or microorganisms.

In some embodiments of the present invention, the essential gene products described herein are used in methods of identifying a target on which a compound that inhibits cellular proliferation acts. Such methods are described in the U.S. Patent Application entitled METHODS FOR IDENTIFYING THE TARGET OF A COMPOUND WHICH INHIBITS CELLULAR PROLIFERATION, filed February 8, 2002. As employed herein, some embodiments of methods used to identify a target on which a compound that inhibits cellular proliferation acts utilize collections or cultures of strains comprising strains which either overexpress a different gene product which is required for cellular proliferation (such as the gene products described herein) or underexpress a different gene product (such as the gene products described herein) which is required for cellular proliferation (i.e. at least some of the strains in the culture overexpress or underexpress a gene product required for cellular proliferation). In some embodiments, the present invention uses collections or cultures of strains comprising both strains which overexpress gene products required for cellular proliferation and strains which underexpress the same gene products required for cellular proliferation. Preferably, each of the strains present in the culture or collection either overexpresses or underexpresses a different gene product which is required for cellular proliferation (i.e. all of the strains in the culture overexpress or underexpress a gene product required for cellular proliferation). However, in some embodiments, the culture or collection may include one or more strains which do not overexpress or underexpress a gene product which is required for proliferation. The gene product which is overexpressed or underexpressed in each strain may be any gene product which is required for cellular prolifereation, including a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581, a gene product whose activity or level is inhibited by a homologous

antisense nucleic acid, a gene product encoded by a homologous coding nucleic acid, and a gene product comprising a homologous polypeptide.

As used herein the term "culture" refers to a plurality of strains growing in a single aliquot of a liquid growth medium and the term "collection" refers to a plurality of strains each of which is growing in a separate aliquot of liquid growth medium or a different location on a solid growth medium.

In some embodiments, if desired, one or more of the strains in the culture or collection of strains may overexpress or underexpress more than one gene product described herein which is required for cellular proliferation. In this embodiment, the gene products which are overexpressed or underexpressed in one or more of the strains may be functionally related or functionally unrelated. This may facilitate the identification of compounds when two or more gene products share similar functions in the cell or where the cell has multiple biochemical pathways which lead to a particular end product.

Alternatively, if the gene product described herein to be overexpressed or underexpressed is encoded by a gene which is part of an operon containing a plurality of genes, the desired gene may be overexpressed or underexpressed while the remaining genes in the operon are expressed at levels where they do not impact the ability of the cell to grow in the presence of a particular compound. For example, the desired gene may be placed under the control of a regulatable promoter, a transcriptional terminator may be placed 3' of the desired gene and a promoter, preferably a constitutive promoter, may be placed 3' of the transcriptional terminator and 5' of the remaining genes in the operon.

In some embodiments, the culture or collection of strains may comprise a strain which overexpresses or underexpresses a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213. In some embodiments, the culture or collection of strains may comprise strains which in aggregate overexpress or underexpress at least two gene products whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOS.: 1-6213, at least 10 gene products whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOS.: 1-6213, at least 20 gene products whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOS.: 1-6213, at least 30 gene products whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOS.: 1-6213, at least 50 gene products whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOS.: 1-6213, at least 100 gene products whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOS.: 1-6213, at least 300 gene products whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOS.: 1-6213 or more than 300 gene products whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOS.: 1-6213, wherein each strain in the culture or collection of strains overexpresses or underexpresses a single gene

product whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs. 1-6213. Alternatively, if desired, one or more of the strains in the culture or collection of strains may overexpress or underexpress more than one gene product whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs. 1-6213.

In other embodiments, the culture or collection of strains may comprise a strain which overexpresses or underexpresses a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397. In some embodiments, the culture or collection of strains may comprise strains which in aggregate overexpress or underexpress at least two gene products encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, at least 10 gene products encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, at least 20 gene products encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, at least 30 gene products encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, at least 50 gene products encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, at least 100 gene products encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, at least 300 gene products encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397 or more than 300 gene products encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, wherein each strain in the culture or collection of strains overexpresses or underexpresses a single gene product encoded by a nucleic acid selected from the group consisting of SEQ ID NOs. 6214-42397. Alternatively, if desired, one or more strains in the culture or collection of strains may overexpress or underexpress more than one gene product encoded by a nucleic acid selected from the group consisting of SEQ ID NOs. 6214-42397.

In some embodiments the culture or collection of strains comprises a strain in which a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581 is overexpressed or underexpressed. In some embodiments, the culture or collection of strains may comprise strains which in aggregate overexpress or underexpress at least two gene products comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581, at least 10 gene products comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581, at least 20 gene products comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581, at least 30 gene products comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581, at least 50 gene products comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581, at least 100 gene products comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581, at least 300 gene

products comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581 or more than 300 gene products comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581, wherein each strain in the culture or collection of strains overexpresses or underexpresses a single gene product selected from the group consisting of SEQ ID NOs. 42938-78581. Alternatively, if desired one or more of the strains in the culture or collection of strains may overexpress or underexpress more than one gene product selected from the group consisting of SEQ ID NOs. 42938-78581.

In other embodiments, the culture or collection of strains comprises a strain in which at least one of the gene products encoded by a homologous coding nucleic acid as defined above is overexpressed or underexpressed. In some embodiments, the culture or collection of strains may comprise strains which in aggregate overexpress or underexpress at least 2, at least 10, at least 20, at least 30, at least 50, at least 100, at least 300 or more than 300 gene products encoded by a homologous coding nucleic acid as defined above. If desired the culture or collection of strains may comprise one or more strains which overexpress or underexpress more than one gene product encoded by a homologous coding nucleic acid. In further embodiments, the culture or collection of strains comprises a strain in which at least one, at least 10, at least 20, at least 30, at least 50, at least 100, at least 300 or more than 300 homologous polypeptides as defined above is overexpressed or underexpressed. If desired the culture or collection of strains may comprise one or more strains which overexpress or underexpress more than one homologous polypeptide.

For example, in some embodiments, the culture or collection of strains comprises a strain in which at least one gene product selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213 is overexpressed or underexpressed, wherein each strain overexpresses or underexpresses one gene product. In some

embodiments, the culture or collection of strains may comprise strains in which in aggregate at least 2, at least 10, at least 20, at least 30, at least 50, at least 100, at least 300, or more than 300 gene products selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213 is overexpressed or underexpressed, wherein each strain overexpresses or underexpresses one gene product.

If desired, one or more of the strains in the culture or collection of strains may overexpress or underexpress more than one gene product selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213.

In further embodiments, the culture or collection of strains comprises a strain in which at least one gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate conditions is overexpressed or underexpressed, wherein each strain overexpresses or underexpresses one gene product. In some embodiments, the culture or collection of strains comprises a strain or a group of strains in which in aggregate at least 2, at least 10, at least 20, at least 30, at least 50, at least 100, at least 300, or more than 300 gene products encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate conditions is overexpressed or underexpressed, wherein each strain overexpresses or underexpresses one gene product.

If desired, one or more of the strains in the culture or collection of strains may overexpress or underexpress more than one gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate conditions.

In additional embodiments, the culture or collection of strains comprises a strain in which at least one gene product comprising a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42938-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is overexpressed or underexpressed, wherein each strain overexpresses or underexpresses one gene product. In some embodiments, the culture or collection of strains comprises a strain or a group of strains in which in aggregate at least 2, at least 10, at least 20, at

least 30, at least 50, at least 100, at least 300, or more than 300 gene products comprising a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42938-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is overexpressed or underexpressed, wherein each strain overexpresses or underexpresses one gene product.

If desired, one or more of the strains in the culture or collection of strains may overexpress or underexpress more than one polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42938-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581.

The methods of the present invention may be used to identify the targets of compounds which inhibit the proliferation of any desired cell or organism. In some embodiments, these methods are employed to identify the targets of compounds which inhibit the proliferation of bacteria, fungi, or protozoans. In further embodiments, these methods are employed to identify the targets of compounds which inhibit the growth of an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* or any species falling within the genera of any of the above species.

Overexpression may be obtained using a variety of techniques familiar to those skilled in the art. For example, overexpression may be obtained by operably linking a gene encoding a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581, a gene product whose activity or level is inhibited by a homologous antisense nucleic acid, a gene product encoded by a homologous coding nucleic acid, or a gene product comprising a homologous polypeptide to a promoter which transcribes a higher level of mRNA encoding or comprising the gene product than does a wild type cell.

A variety of promoters may be used to overexpress the gene product described herein, including a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581, a gene product whose activity or level is inhibited by a homologous antisense nucleic acid, a gene product encoded by a homologous coding nucleic acid, and a gene product comprising a homologous polypeptide. The promoters used to overexpress the gene product may be relatively strong promoters, promoters which possess a moderate level of activity, or relatively weak promoters and may be either constitutive or regulatable promoters. In some embodiments, several strains, each of which overexpresses the gene product to a different extent, may be used in order to optimize the degree of overexpression of the gene product.

In some embodiments, each of the gene products required for proliferation may be placed under the control of several different promoters of varying strengths to create several different strains which express the gene product at varying levels. The level of expression of the gene product in each of the strains is compared to that in wild type cells in order to identify a promoter which provides a desired level of expression relative to wild type cells (i.e. a desired level of overexpression or underexpression). The strain having the desired level of expression is then included in a culture or collection of strains to be contacted with a test compound as discussed below. Examples of suites of regulatable promoters having varying strengths that are useful for the expression of gene products at varying levels are described in U.S. Patent Application Serial Number 10/032,393, filed on December 21, 2002.

The promoter is selected to be active in the type of cell in which the gene product is to be expressed. For example, for overexpression of the gene product in mammalian cells, the gene encoding the gene product may be operably linked to promoters such as the SV40 promoter, the metallothionine promoter, the MMTV promoter, the RSV promoter, the tetP promoter, the adenovirus major late promoter or other promoters known to those skilled in the art. In yeast, the gene encoding the gene product may be operably linked to promoters such as the CYC1, ADHI,

ADHII, GAL1, GAL10, PHO5, PGK or other promoters used in the art. Similarly, in bacteria, the gene encoding the gene product may be operably linked to the , SP6, T3, trc promoter, lac promoter, temperature regulated lambda promoters, the *Bacillus* aprE and nprE promoters (U.S. Patent No. 5,387,521), the bacteriophage lambda P_L and P_R promoters (Renaut, et al., (1981) Gene 15: 81) the trp promoter (Russell, et al., (1982) Gene 20: 23), the tac promoter (de Boer et al., (1983) Proc. Natl. Acad. Sci. USA 80: 21), *B. subtilis* alkaline protease promoter (Stahl et al, (1984) J. Bacteriol. 158, 411-418) alpha amylase promoter of *B. subtilis* (Yang et al., (1983) Nucleic Acids Res. 11, 237-249) or *B. amyloliquefaciens* (Tarkinen, et al, (1983) J. Biol. Chem. 258, 1007-1013), the neutral protease promoter from *B. subtilis* (Yang et al, (1984) J. Bacteriol. 160, 15-21), T7 RNA polymerase promoter (Studier and Moffatt (1986) J Mol Biol. 189(1):113-30), *B. subtilis xyl* promoter or mutant tetR promoter active in bacilli (Geissendorfer & Hillen (1990) Appl. Microbiol. Biotechnol. 33:657-663), Staphylococcal enterotoxin D promoter (Zhang and Stewart (2000) J. Bacteriol. 182(8):2321-5), cap8 operon promoter from *Staphylococcus aureus* (Ouyang et al., (1999) J. Bacteriol. 181(8):2492-500), the lactococcal nisA promoter (Eichenbaum (1998) Appl Environ Microbiol. 64(8):2763-9), promoters from in *Acholeplasma laidlawii* (Jarhede et al., (1995) Microbiology 141 (Pt 9):2071-9), porA promoter of *Neisseria meningitidis* (Sawaya et al., (1999) Gene 233:49-57), the fbpA promoter of *Neisseria gonorrhoeae* (Forng et al., (1997) J. Bacteriol. 179:3047-3052), *Corynebacterium diphtheriae* toxin gene promoter (Schmitt and Holmes (1994) J. Bacteriol. 176(4):1141-9), the hasA operon promoter from Group A Streptococci (Alberti et al., (1998) Mol Microbiol 28(2):343-53), the rpoS promoter of *Pseudomonas putida* (Kojic and Venturi (2001) J. Bacteriol. 183:3712-3720), the *Acinetobacter baumannii* phosphate regulated *ppk* gene promoter (Gavigan et al., Microbiology 145:2931-7 (1999)); the *Acinetobacter baumannii adhC1* promoter which is induced under iron limitation and repressed when the cells are cultured in the presence of free inorganic iron (Echenique et al., Microbiology 147:2805-15 (2001)); the *flaB* promoter of pGK12 active in *Borrelia burgdorferi* (Sartakova et al., Proc Natl Acad Sci U S A. 97(9):4850-5 (2000)); the use of Ptrc promoter results in strong inducer-dependent expression in *Burkholderia spp* (Santos et al., FEMS Microbiol Lett 195(1):91-6 (2001)); the iron regulated *sodA* promoter of *Bordetella pertussis* (Graeff-Wohlleben et al., J Bacteriol 179(7):2194-201 (1997)); UV-inducible bcn and uviAB promoters in *Clostrdia spp* (Garnier and Cole Mol Microbiol 2(5):607-14 (1988)); the heat-inducible *clpB* promoter of *Campylobacter jejuni* (Thies et al., Gene 230(1):61-7 (1999)); promoters carrying bacteriophage C1 operator sites in *Klebsiella pneumoniae* (Schoefield et al, J Bacteriol 183(23):6947-50 (2001)); the *Proteus mirabilis ureR* promoter (Poore et al., J Bacteriol 183(15):4526-35 (2001)); and the heat-inducible *groESL* promoter in *Listeria monocytogenes*, and the IPTG inducible promoter in pLEX5BA (Krause et al., J. Mol. Biol. 274: 365 (1997). In another embodiment, which may be useful in *Staphylococcus aureus*, the promoter is a novel inducible promoter system, XylT5, comprising a modified T5 promoter fused to the *xylO* operator from the *xylA* promoter of *Staphylococcus aureus*. This promoter is described in U.S. Patent Application Serial Number 10/032,393. In another embodiment the promoter may be a two-

component inducible promoter system in which the T7 RNA polymerase gene is integrated on the chromosome and is regulated by *lac*UV5/ *lac*O (Brunschwig, E. and Darzins, A. 1992. Gene 111:35-41, and a T7 gene 10 promoter, which is transcribed by T7 RNA polymerase, is fused with a *lac*O operator. In another embodiment the promoter may be the promoters from the plasmids pEPEF3 or pEPEF14, which harbor xylose inducible promoters functional in *E. faecalis*, described in U.S. Patent Application Serial No. 10/032,393. Other promoters which may be used are familiar to those skilled in the art. In fungi, the gene encoding the gene product may be operably linked to the CaACT1 promoter (Morschhauser, Mol. Gen. Genet. 257: 412-420 (1998), or other promoters familiar to those skilled in the art. It will appreciated that other combinations of organisms and promoters may also be used in the present invention.

In some embodiments, overexpression may be achieved by using homologous recombination to replace the natural promoter which drives expression of the proliferation-required genes described herein with a regulatable promoter. For example, the methods described in U.S. Patent Application 09/948,993 may be used to place the gene required for proliferation under the control of a regulatable promoter. Examples of gene products, which are encoded by genes that can be overexpressed by regulatable promoters introduced by such promoter replacement methods include a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581, a gene product whose activity or level is inhibited by a homologous antisense nucleic acid, a gene product encoded by a homologous coding nucleic acid, and a gene product comprising a homologous polypeptide.

Briefly, in some embodiments of these methods in which natural promoters are replaced by regulatable promoters, the cells may be haploid, such as bacterial cells. Regulatable promoters that are useful for promoter replacement in bacterial cells include, but are not limited to, the promoters described in U.S. Patent Application Serial Number 10/032,393 filed December 21, 2001. A linear promoter replacement cassette comprising a regulatable promoter flanked by nucleotide sequences having homology to the natural promoter is introduced into the cell. In some embodiments, the cassette also comprises a nucleotide sequence encoding a selectable marker or a marker whose expression is readily identified. The cassette may be a double stranded nucleic acid or a single stranded nucleic acid as described in U.S. Patent Application Serial Number 09/948,993. Upon homologous recombination, the natural promoter is replaced with the regulatable promoter, leaving the gene required for proliferation under the control of the regulatable promoter. Strains in which the gene required for proliferation is under control of the regulatable promoter are grown under conditions in which the regulatable promoter provides a level of the proliferation-required gene product which is above the level in a wild type cell. For example, the strains may be grown in the

presence of an inducer which induces expression from the regulatable promoter, or under conditions in which the action of a repressor on the regulatable promoter is reduced or eliminated.

Alternatively, rather than replacing the native promoters of each of the genes encoding a proliferation-required gene product described herein with a single desired replacement promoter, a plurality of replacement promoters which provide desired expression levels for the gene products to be overexpressed or underexpressed are used. The method is performed as described above except that rather than using a single labeled primer complementary to a nucleotide sequence within the single replacement promoter, a plurality of labeled primers complementary to suitable nucleotide sequences in the plurality of replacement promoters are used.

Alternatively, in embodiments in which the level or activity of proliferation-required gene products described herein is reduced by transcribing an antisense nucleic acid complementary to at least a portion of the genes encoding such gene products, the strains may be designed such that the length of the nucleotide sequence encoding the antisense nucleic acid is different for each gene. Amplification reactions are performed as described above using primers at each end of the gene encoding the antisense nucleic acid such that the amplification product corresponding to each gene has a unique length or a dye which allows it to be distinguished from other amplification products of the same length. Alternatively, the lengths of the nucleotide sequences encoding the antisense nucleic acids may not be unique for each gene, but the primers used in the amplification reaction may be selected such that the length of the amplification product corresponding to each gene is unique.

In another embodiment, the native promoters may be replaced with promoters which include therein or adjacent thereto a unique nucleotide sequence which is distinct from that present in the other replacement promoters in the strains in the culture or collection of strains. In this embodiment, each promoter includes or has adjacent thereto a unique "tag" which may be used to identify strains which proliferate more rapidly or more slowly in the culture or collection of strains. The tag may be detected using hybridization based methods or amplification based methods, including the amplification method which generates amplification products having a unique size for each proliferation required gene described above.

Alternatively, the native promoter which directs the transcription of the proliferation-required genes described herein may rendered regulatable by inserting a regulatory element into the chromosome of the cell via homologous recombination such that the regulatory element regulates the level of transcription from the promoter. Examples of gene products, which are encoded by genes that have promoters which can be rendered regulatable by regulatory elements inserted by such methods include a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581, a gene product whose activity or

level is inhibited by a homologous antisense nucleic acid, a gene product encoded by a homologous coding nucleic acid, and a gene product comprising a homologous polypeptide.

A variety of regulatory elements may be used to regulate the expression of essential gene products described herein. The regulatory element may be an operator which is recognized by a repressor (e.g. lac, tet, araBAD repressors) or a nucleotide sequence which is recognized by a transcriptional activator. In some embodiments, the regulatory element may be a transcriptional terminator, a nucleotide sequence which introduces a bend in the DNA or an upstream activating sequence. A linear regulatory element insertion cassette comprising a regulatory element flanked by nucleotide sequences having homology to the natural promoter is introduced into the cell. In some embodiments, the cassette also comprises a nucleotide sequence encoding a selectable marker or a marker whose expression is readily identified. The cassette may be a double stranded nucleic acid or a single stranded nucleic acid as described in U.S. Patent Application Serial Number 09/948,993. Upon homologous recombination, the regulatory element is inserted into the chromosome, leaving the gene required for proliferation under the control of the regulatory element. Strains in which the gene required for proliferation is under control of the regulatory element are grown under conditions in which the regulatable promoter provides a level of the proliferation-required gene product which is above the level in a wild type cell. For example, the strains may be grown in the presence of an inducer which induces expression from the promoter, or under conditions in which the action of a repressor on the promoter is reduced or eliminated. It will be appreciated that the amplification method which generates amplification products having a unique size for each proliferation required gene may be used to detect strains which are overrepresented or underrepresented in the culture or collection of strains. For example, if desired, primers complementary to a nucleotide sequence within the regulatory element may be used in the amplification reaction.

The promoter replacement cassette or regulatory element insertion cassette may be a double stranded nucleic acid, such as an amplicon generated through PCR or other amplification methods, or a single stranded nucleic acid, such as an oligonucleotide. For example, single stranded nucleic acids may be introduced into the chromosome using the methods described in Ellis et al., PNAS 98: 6742-6746, 2001.

In some embodiments, the cell into which the promoter replacement cassette or regulatory element insertion cassette is introduced has an enhanced frequency of recombination. For example, the cells may lack or have a reduced level or activity of one or more exonucleases which would ordinarily degrade the DNA to be inserted into the chromosome. In further embodiments, the cells may both lack or have reduced levels of exonucleases and express or overexpress proteins involved in mediating homologous recombination. For example, if the methods are performed in *Escherichia coli* or other enteric prokaryotes, cells in which the activity of exonuclease V of the RecBCD recombination pathway, which degrades linear nucleic acids, has been reduced or eliminated, such as recB, recC, or recD mutants may be used. In some embodiments, the cells have

mutations in more than one of the recB, recC, and recD genes which enhance the frequency of homologous recombination. For example the cells may have mutations in both the recB and recC genes.

The promoter replacement or regulatory element insertion methods may also be performed in *Escherichia coli* cells in which the activity of the RecET recombinase system of the Rac prophage has been activated, such as cells which carry an sbcA mutation. The RecE gene of the rac prophage encodes ExoVIII a 5'-3' exonuclease, while the RecT gene of the Rac prophage encodes a single stranded DNA binding protein which facilitates renaturation and D-loop formation. Thus, the gene products of the RecE and RecT genes or proteins with analogous functions facilitate homologous recombination. The RecE and RecT genes lie in the same operon but are normally not expressed. However, sbcA mutants activate the expression the RecE and RecT genes. In some embodiments, the methods may be performed in cells which carry mutations in the recB and recC genes as well as the sbcA mutation. The RecE and RecT gene may be constitutively or conditionally expressed. For example, the methods may be performed in *E. coli* strain JC8679, which carries the sbcA23, recB21 and recC22 mutations.

In some embodiments, the methods may be performed in *Escherichia coli* cells in which recombination via the RecF pathway has been enhanced, such as cells which carry an sbcB mutation.

It will be appreciated that the RecE and RecT gene products, or proteins with analogous functions may be conditionally or constitutively expressed in prokaryotic organisms other than *E. coli*. In some embodiments, these proteins may be conditionally or constitutively expressed in *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei,*

Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis or any species falling within the genera of any of the above species. For example, plasmids encoding these gene products may be introduced into the organism. If desired, the coding sequences encoding these gene products may be optimized to reflect the codon preferences of the organism in which they are to be expressed. Similarly, in some embodiments, the organism may contain mutations analogous to the recB, recC, recD, sbcA or sbcB mutations which enhance the frequency of homologous recombination.

In further embodiments, the promoter replacement or regulatory element insertion methods may be conducted in cells which utilize the Red system of bacteriophage lambda (λ) or analogous systems from other phages to enhance the frequency of homologous recombination. The Red system contains three genes, (γ, β and *exo* whose products are the Gam, Bet and Exo proteins (see Ellis et al. PNAS 98:6742-6746, 2001. The Gam protein inhibits the RecBCD exonuclease V, thus permitting Beta and Exo to gain access to the ends of the DNA to be integrated and facilitating homologous recombination. The Beta protein is a single stranded DNA binding protein that promotes the annealing of a single stranded nucleic acid to a complementary single stranded nucleic acid and mediates strand exchange. The Exo protein is a double-stranded DNA dependent 5'-3' exonuclease that leaves 3' overhangs that can act as substrates for recombination. Thus, constitutive or conditional expression of the λ Red proteins or proteins having analogous functions facilitates homologous recombination.

It will be appreciated that the λ Beta, Gam and Exo proteins, or proteins with analagous functions may be expressed constitutively or conditionally in prokaryotic organisms other than *E. coli*. In some embodiments, these proteins may be conditionally or constitutively expressed in *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma eapsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris,*

Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis or any species falling within the genera of any of the above species. For example, plasmids encoding these gene products may be introduced into the organism. If desired, the coding sequences encoding these gene products may be optimized to reflect the codon preferences of the organism in which they are to be expressed.

In some embodiments, the cells may have an increased frequency of homologous recombination as a result of more than one of the aforementioned characteristics. In some embodiments, the enhanced frequency of recombination may be a conditional characteristic of the cells which depends on the culture conditions in which the cells are grown. For example, in some embodiments, expression of the λ Red Gam, Exo, and Beta proteins or recE and recT proteins may be regulated. Thus, the cells may have an increased frequency of homologous recombination as a result of any combination of the aforementioned characteristics. For example, in some embodiments, the cell may carry the sbcA and recBC mutations.

In some embodiments, a linear double stranded DNA to be inserted into the chromosome of the organism is introduced into an organism constitutively or conditionally expressing the recE and recT or the λ Beta, Gam and Exo proteins or proteins with analogous functions as described above. In some embodiments, the organism may be *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei,*

Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis or any species falling within the genera of any of the above species. In some embodiments, the double stranded DNA may be introduced into an organism having the recBC and sbcA mutations or analogous mutations.

In other embodiments, a single stranded DNA to be inserted into the chromosome of the organism is introduced into an organism expressing the λ Beta protein or a protein with an analogous function. In some embodiments the single stranded DNA is introduced into an organism expressing both the λ Beta and Gam proteins or proteins with analogous functions. In further embodiments, the single stranded DNA is introduced into an organism expressing the λ Beta, Gam and Exo proteins or proteins with analogous functions. The λ proteins or analogous proteins may be expressed constitutively or conditionally. In some embodiments, the organism may be *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* or any species falling within the genera of any of the above species.

In some embodiments, the linear nucleic acid may be introduced into the chromosome of a first organism which has an enhanced frequency of homologous recombination and then transferred to a second organism which is less amenable to direct application of the present methods. For example, the linear nucleic acid may be introduced into the chromosome of *E. coli* and transferred

into a second organism via conjugation or transduction. After introduction into the second organism, the nucleic acid is inserted into the chromosome of the second organism via homologous recombination, thereby effectively transferring the regulatory element from the chromosome of the first organism into the corresponding location in the chromosome of the second organism.

In other embodiments, the cells may be diploid cells, such as fungal cells. In some embodiments, one copy of the gene encoding the proliferation-required gene product may be disrupted, rendering it inactive. In further embodiments, one copy of the gene encoding the proliferation-required gene product may be disrupted and the other copy of the gene encoding the proliferation-required gene product may be placed under the control of a regulatable promoter. Such strains may be generated by disrupting the first copy of the gene encoding the proliferation-required gene product by homologous recombination using a disruption cassette comprising a nucleotide sequence encoding an expressible dominant selectable marker flanked on each side by nucleic acids homologous to the target sequence to be disrupted. The second copy of the gene encoding the proliferation-required gene product may be placed under the control of a regulatable promoter by homologous recombination using a promoter replacement cassette comprising a regulatable promoter flanked on each side by nucleic acids homologous to the natural promoter for the proliferation-required gene. The promoter replacement cassette may also include a nucleotide sequence encoding a selectable marker located 5' of the regulatable promoter but between the nucleic acids homologous to the natural promoter.

In other embodiments, overexpression may be achieved by operably linking a proliferation-required gene product described herein to a desired promoter in a vector. The vector may be a vector which replicates extrachromosomally or a vector which integrates into the chromosome. For example, if the vector is to be used in bacterial cells, the vector may be a pBR322 based vector or a bacteriophage based vector such as P1 or lambda. If the vector is to be used in *Saccharomyces cerevisae*, it may be a vector based on the 2 micron circle or a vector incorporating a yeast chromosomal origin of replication. If the vector is to be used in mammalian cells, it may be a retroviral vector, SV40 based vector, a vector based on bovine papilloma virus, a vector based on adenovirus, or a vector based on adeno-associated virus. If the vector is to be used in *Candida albicans* it may be a vector comprising a promoter selected from the group consisting of the CaPCK1, MET25, MAL2, PHO5, GAL1,10, STE2 or STE3 promoters. In some embodiments, the vectors described in the following publications may be used: CIp10, an efficient and convenient integrating vector for *Candida albicans*. Murad et al., Yeast 16(4):325-7 (2000); Transforming vector pCPW7, Kvaal et al., : Infect Immun 67(12):6652-62 (1999); Transforming vector pCWOP16, Kvaal et al., : Infect Immun 65(11):4668-75 (1997); double-ARS vector, pRM1, to be used for direct cloning in Ca by complementation of the histidine auxotrophy of strain CA9, Pla et al., Gene 165(1):115-20 (1995); pMK16, that was developed for the transformation of *C. albicans* and carries an ADE2 gene marker and a *Candida* autonomously replicating sequence (CARS) element promoting autonomous replication (cited in Sanglard and Fiechter Yeast 8(12):1065-75

(1992); A plasmid vector (denoted pRC2312) was constructed, which replicates autonomously in *Escherichia coli, Saccharomyces cerevisiae* and *Candida albicans*. It contains LEU2, URA3 and an autonomously replicating sequence (ARS) from *C. albicans*, Cannon et al., Mol Gen Genet 235(2-3):453-7 (1992); Expression vector (CIp10-MAL2p) for use in *Candida albicans* has been constructed in which a gene of interest can be placed under the control of the CaMAL2 maltase promoter and stably integrated at the CaRP10 locus (Backen et al., Yeast 16(12):1121-9 (2000)); (Volker, R. S., A. Sonneborn, C. E. Leuker, and J. F. Ernst. 1997. Efg1p, an essential regulator of morphogenesis of the human pathogen *Candida albicans*, is a member of a conserved class of bHLH proteins regulating morphogenetic processes in fungi. EMBO **16**:1982-1991.); and a *C. albicans* transformation vector containing the *C. albicans* URA3 gene, a Candida ARS sequence, and a portion of the *Saccharomyces cerevisiae* 2 microns circle containing the replication origin was constructed. Goshorn et al., Infect Immun 60(3):876-84 (1992). A variety of other vectors suitable for use in foregoing organisms or in any other organism in which the present invention is to be practiced are familiar to those skilled in the art.

Underexpression of a proliferation-required gene product described herein may be obtained in a variety of ways. For example, in one embodiment underexpression of the proliferation-required gene product may be achieved by providing an agent, such as an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, an antisense nucleic acid comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a nucleic acid complementary to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, a nucleic acid complementary to a nucleic acid comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, a nucleic acid complementary to a nucleic acid which encodes a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581, a nucleic acid complementary to a nucleic acid which encodes at least 5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, or 150 consecutive amino acids of a polypeptide sequence selected from the group consisting of SEQ ID NOs.: 42398-78581, a homologous antisense nucleic acid, an antisense nucleic acid comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of a homologous nucleic acid, a nucleic acid complementary to a homologous coding nucleic acid, a nucleic acid complementary to at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of a homologous coding nucleic acid, a nucleic acid complementary to a nucleic acid which encodes a homologous polypeptide, or a nucleic acid complementary to a nucleic acid which encodes at least 5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, or 150 consecutive amino acids of a homologous polypeptide, which reduces the level or activity of the gene product within the cell. In one embodiment, the agent may comprise an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ

ID NOs.: 1-6213 which is complementary to a nucleic acid encoding the proliferation-required gene product or complementary to a portion of a nucleic acid encoding the proliferation-required gene product.

In one example of antisense-inhibition-based underexpression, a nucleic acid which encodes the antisense nucleic acid may be operably linked to a regulatable promoter. When grown under appropriate conditions, such as media containing an inducer of transcription or an agent which alleviates repression of transcription, the antisense nucleic acid is expressed in the cell, thereby reducing the level or activity of the gene product within the cell. In some embodiments, the concentration of the inducer of transcription or the agent which alleviates repression of transcription may be varied to provide optimal results. Such methods have been described previously herein and in U.S. Patent Application Serial Number 09/815,242, U.S. Patent Application Serial Number 09/492,709, U.S. Patent Application Serial Number 09/711,164, or U.S. Patent Application Serial Number 09/741,669.

Alternatively, underexpression of a proliferation-required gene product described herein may be achieved by constructing strains in which the expression of the gene product is under the control of a constitutive or regulatable promoter using methods such as those described above with respect to methods in which the gene product is overexpressed. To provide cells which underexpress the gene product, the cells are grown under conditions in which the gene product is expressed at a level lower than that of a wild type cell. For example, the cells may be grown under conditions in which a repressor reduces the level of transcription from the regulatable promoter.

In other embodiments, underexpression may be achieved by operably linking the gene required for proliferation to a desired promoter in a vector as described above with respect to embodiments in which gene products required for proliferation are overexpressed. In some embodiments, the vector may be present in cells in which the chromosomal copy or copies of the gene has been disrupted.

Examples of gene products, which are encoded by genes that can be underexpressed using methods such as those described above with respect to methods in which the gene product is overexpressed include a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581, a gene product whose activity or level is inhibited by a homologous antisense nucleic acid, a gene product encoded by a homologous coding nucleic acid, and a gene product comprising a homologous polypeptide.

One embodiment of the invention includes a method for identifying a gene product described herein on which a compound which inhibits the proliferation of an organism acts. The method employs a culture which comprises a mixture of strains of the organism. At least some of the strains in the culture overexpress a different gene product which is required for the proliferation

of the organism. Preferably, each of the strains in the culture overexpresses a different gene product which is required for proliferation of the organism (i.e. all of the strains in the culture overexpress a gene product which is required for proliferation of the organism). For example, the gene product which is overexpressed in each strain may be a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581, a gene product whose activity or level is inhibited by a homologous antisense nucleic acid, a gene product encoded by a homologous coding nucleic acid, and a gene product comprising a homologous polypeptide.

Strains that overexpress the proliferation-required gene product may be obtained using the methods described above. The culture may comprise any number of strains which overexpress a gene product required for proliferation. For example the culture may comprise at least two strains, at least 10 strains, at least 20 strains, at least 30, strains, at least 50 strains, at least 100 strains, at least 300 strains or more than 300 strains which overexpress a gene product required for proliferation. In some embodiments, the culture may comprise strains which in aggregate overexpress all or most of the gene products required for proliferation of the organism.

The culture is contacted with a compound which inhibits proliferation of the organism. The compound may be a candidate drug compound obtained from any source. For example, the compound may be a compound generated using combinatorial chemistry, a compound from a natural product library, or an impure or partially purified compound, such as a compound in a partially purified natural extract. The culture is contacted with a sufficient concentration of the compound to inhibit the proliferation of strains of the organism in the culture which do not overexpress the gene product on which the compound acts, such that strains which overexpress said gene product on which the compound acts proliferate more rapidly in the culture than strains which do not overexpress said gene product on which said compound acts. Thus, after a sufficient period of time, the strain which overexpresses the gene product on which the compound acts will be more prevalent in the culture than strains which do not overexpress the gene product on which the compound acts. In a preferred embodiment, the growth conditions and incubation period are selected so that only one strain, the strain overexpressing the target of the compound, is recovered from the culture. Thus, in one embodiment, a plurality of cultures containing a plurality of strains each of which overexpresses a different proliferation-required gene product may be grown in the presence of varying concentrations of the compound. In addition to varying the compound concentrations, in embodiments where expression of the proliferation-required gene product is under the control of a regulatable promoter, the plurality of cultures may be grown at varying concentrations of an agent which regulates the level of expression from the promoter, such as an inducer or an agent which reduces the effect of a repressor on transcription from the promoter. It

will be appreciated, that the cultures may be grown in liquid medium in the presence of the compound whose target is to be identified (and where appropriate in the presence of an agent which regulates the level of expression from the promoter) or alternatively, a liquid culture comprising the strains which overexpress the proliferation-required gene products may be grown in the absence of the compound whose target is to be identified and then introduced onto a solid medium containing the compound (and, where appropriate, also containing an agent which regulates the level of expression from the promoter).

The identity of the overexpressed gene product which is the target of the compound may be determined using a variety of methods. For example, in some embodiments of the present invention, the nucleic acids present in the culture or collection of strains which was contacted with the compound may be compared to the nucleic acids present in a control culture or collection of strains which was not contacted with the compound to identify nucleic acids which are overrepresented in the culture or collection of strains contacted with the test compound relative to the control culture or collection of strains. Alternatively, in some embodiments, the nucleic acids present in a culture or collection of strains contacted with the test compound may be analyzed to identify those nucleic acids which are present without comparison to a control culture or collection of strains.

In some embodiments, the strains which proliferated more rapidly in the culture or collection of strains, i.e. strains having an enhanced ability to proliferate in the presence of a test compound relative to other strains in the culture or collection of strains, are identified as follows. Amplification products which are correlated with each of the overexpressed genes and which are distinguishable from one another are obtained from a culture or collection grown in the presence of a test compound. The amplification products are distinguished from one another to determine whether a particular amplification product is overrepresented in the culture or collection of strains. In some embodiments, the amplification products corresponding to each of the gene products have lengths which permit them to be distinguished from one another. In another embodiment, one or more of the amplification products have similar or identical lengths but are distinguishable from one another based on a detectable agent, such as a dye, attached thereto. In some embodiments, amplification products which are overrepresented are identified by comparing the amplification products from the culture or collection of strains which was contacted with the test compound to the amplification products from a culture or collection of strains which was not contacted with the test compound. Alternatively, amplification products which are overrepresented may be identified by simply identifying the amplification products obtained from the culture or collection of strains contacted with the test compound (for example, only one or a few strains may have proliferated in the presence of the test compound). The above methods for generating distinguishable amplification products may be used in conjunction with any of the methods for generating strains which overexpress gene products required for proliferation described herein in order to facilitate the

identification of strains which proliferate more rapidly or more slowly in the presence of a test compound.

For example, in some embodiments of the present invention, each of the native promoters of each of the genes encoding gene product required for proliferation are replaced by a single desired replacement promoter. After growth of the culture or collection of strains containing the strains in which the promoters have been replaced in the presence of a test compound for a desired period of time, an amplification reaction is performed on nucleic acids obtained from the culture as follows.

The nucleic acids from the culture or collection of strains may be divided into at least two aliquots if desired. In a preferred embodiment the nucleic acids from the culture or collection of strains are divided into four aliquots. A single primer complementary to a nucleotide sequence within the replacement promoter , within the proliferation required genes, or within nucleic acid sequences adjacent to the promoter or proliferation required genes is divided into at least two portions, one portion for each aliquot of nucleic acids. Each portion of the primer is labeled with a distinct detectable dye, such as the 6FAM™, TET™, VIC™, HEX™, NED™, and PET™ dyes obtainable from Applied Biosystems (Foster City, CA). For example, the DS-31 or DS-33 dye sets available from Applied Biosystems (Foster City, CA) may be used to label the primers. Alternatively, the HEX™, NED, JOE, TMR and TET™ dyes available from Amersham Biosciences may be used. Thus, if the nucleic acids from the culture are not divided into aliquots, a single primer labeled with a single dye may be used. If the nucleic acids from the culture are divided into aliquots, at least 2, at least 3, at least 4 or more than 4 primers labeled with distinguishable dyes may be used. Each of the portions of labeled primers are added to each of the aliquots of the nucleic acids from the culture or collection of strains such that each aliquot of nucleic acid receives a single labeled primer with a single detectable dye thereon. In some embodiments, the primers are divided into 3 portions, 4 portions or more than 4 portions, with each portion having a dye which is distinguishable from the dyes on the other portions thereon.

Each of the aliquots of nucleic acids also receives a set of unlabeled primers, with each of the unlabeled primers being complementary to a nucleotide sequence within the promoter, within a nucleotide sequence which is unique to one of the genes encoding gene products required for proliferation which were placed under the control of the replacement promoter, or within nucleotide sequences adjacent to the promoter or proliferation required genes. Each of the aliquots receives primers unique to 1/N proliferation required genes which were placed under the control of the replacement promoter, where N is the number of aliquots (i.e. if the culture or collection of strains consisted of 100 strains in which a gene required for proliferation was placed under the control of the replacement promoter and was divided into four aliquots, then each of the four aliquots of nucleic acids from the culture or collection of strains would receive primers complementary to 25 of the genes). The unlabeled primers are selected so that each will yield an amplification product having a length distinguishable from the length of the amplification product produced with the other

unlabeled primers. Preferably, the amplification products are between about 100-about 400 nucleotides in length, but any lengths which may be distinguished from each other may be used. In addition, in some of the embodiments some of the amplification products may have identical or very similar lengths but be distinguishable from one another due to labeling with distinguishable dyes.

A nucleic acid amplification reaction is conducted on each of the nucleic acid aliquots. The amplification products are then separated by length to identify amplification products having increased representation in the culture or collection of strains (i.e. amplification products derived from cells which proliferated more rapidly in the culture or collection of strains). The amplification products are then correlated with the corresponding genes to determine which strains proliferated more rapidly in the culture or collection of strains. If desired, amplification products having increased representation in the culture may be identified by comparing the amplification products obtained from a culture or collection of strains which was contacted with the compound to amplification products obtained from a control culture or collection of strains which was not contacted with the compound. Alternatively, if desired, the amplification products which are obtained from a culture which was contacted with the compound may be directly identified without comparison to a control culture which was not contacted with the compound.

For example, in some embodiments, the amplification products from each of the nucleic acid aliquots are pooled and subjected to capillary electrophoresis. The amplification products are detected by detecting the fluorescent dyes attached thereto and their lengths are determined to identify those amplification products having increased or decreased representation in the culture or collection of strains. Figures 2A and 2B illustrate one embodiment of this method in which the absence of an amplification product from an amplification reaction performed on a culture comprising a plurality of strains underexpressing genes required for proliferation indicates that a test compound acts on the gene corresponding to the missing amplification product. It will be appreciated that the method may also be used to identify an amplification product which is overrepresented in an amplification reaction conducted on a culture or collection of strains overexpressing genes required for proliferation because the test compound acted on the corresponding gene.

Alternatively, in another embodiment, a first amplification reaction is performed on nucleic acids obtained from a culture or collection of strains which was contacted with the compound using a first primer complementary to a nucleotide sequence present upstream or downstream of all of the overexpressed genes (such as a primer complementary to a nucleotide sequence in a replacement promoter upstream of all of the overexpressed genes) and a set of primers complementary to a nucleotide sequence unique to each of the strains (such as a primer complementary to a nucleotide sequence within each of the proliferation-required genes). One of the two amplification primers for each of the proliferation required genes is labeled with a dye as described above. Preferably, the common primer complementary to a nucleotide sequence upstream or downstream of all of the

overexpressed genes is labeled with the dye. The primers used in the amplification reaction are designed so that the amplification product corresponding to each proliferation-required gene has a unique length or a dye which allows it to be distinguished from other amplification products of the same length. A second amplification reaction is conducted on a control culture or collection of strains which was not contacted with the compound using the same primers as in the first amplification reaction. The amplification products from the first amplification reaction are compared to those from the second amplification reaction to identify one or more amplification products which are overrepresented in the culture or collection of strains. For example, the amplification products from the first amplification reaction may be run in a separate lane of a polyacrylamide gel or a separate capillary than the amplification products from the second amplification reaction and the two lanes or capillaries are compared to one another. If desired, in the embodiment where the amplification products from the first amplification reaction are run in a different lane or capillary than the amplification products from the second amplification reaction, the same dye may be used to label the primers in the first and second amplification reactions. Alternatively, if desired, different dyes may be used to label the primers in the first and second amplification reactions. If desired, in the embodiment where the amplification products from the first amplification reaction are run in a different lane or capillary than the amplification products from the second amplification reaction, the same dye may be used to label the primers in the first and second amplification reactions. Alternatively, if desired, different dyes may be used to label the primers in the first and second amplification reactions.

Alternatively, in some embodiments, the primers in the second amplification reaction are labeled with a different dye which is distinguishable from the dye used in the first amplification reaction. In this embodiment, the amplification reactions may be pooled and run in the same lane on a polyacrylamide gel or in the same capillary and the products from each amplification reaction are compared by comparing the amount of each dye present for each amplification product. Figures 3A and 3B illustrate one embodiment of this method in which the absence of an amplification product from the amplification reaction performed on a culture comprising a plurality of strains underexpressing genes required for proliferation which was contacted with the compound indicates that a test compound acts on the gene corresponding to the missing amplification product. It will be appreciated that the method may also be used to identify an amplification product which is overrepresented in an amplification reaction conducted on a culture or collection of strains overexpressing genes required for proliferation because the test compound acted on the corresponding gene.

If desired, rather than dividing the culture into aliquots, individual amplification reactions may be conducted on nucleic acids obtained from the culture or collection of strains. Each amplification reaction contains primers which will yield an amplification product specific for only one of the proliferation required genes. The resulting amplification products from each of the

individual amplification reactions are pooled and amplification products having increased representation in the culture are identified as described above.

In another embodiment, a culture or collection of strains in which gene products required for proliferation are overexpressed from regulatable promoters which replaced the native promoters of the genes encoding these gene products is allowed to grow in the presence of a test compound for a desired number of generations. Preferably, the culture or collection of strains is allowed to grow in the presence of the test compound for at least 20 generations. Nucleic acids are isolated from the culture or collection of strains and an amplification reaction is performed using a primer which is complementary to a nucleotide sequence within the replacement promoter(s) or a nucleotide sequence adjacent to the a 5' end thereof and primers which are complementary to a nucleotide sequence within the proliferation required genes or nucleotide sequences adjacent thereto. The resulting amplification product(s) is directly sequenced using a primer complementary to a nucleotide sequence within the replacement promoter.

In one embodiment of the present invention, the vector containing the nucleotide sequence encoding the proliferation-required gene product is obtained from a strain which proliferated more rapidly in the culture using methods such as plasmid preparation techniques. Nucleic acid sequencing techniques are then employed to determine the nucleotide sequence of the gene which was overexpressed.

Alternatively, the identity of the overexpressed gene product which is the target of the compound may be determined by performing a nucleic acid amplification reaction, such as a polymerase chain reaction (PCR), to identify the nucleotide sequence of the gene which was overexpressed. For example, aliquots of a nucleic acid preparation, such as a purified plasmid, from the strain which is recovered from the culture may each be contacted with pairs of PCR primers which would amplify a different proliferation-required gene to determine which pair of primers yields an amplification product.

An alternative method for determining the identity of the gene product described herein which is the target of the compound involves obtaining a nucleic acid array, such as a DNA chip, which contains each of the proliferation-required genes which were overexpressed in the strains in the culture. Each proliferation-required gene occupies a known location in the array. A nucleic acid preparation, such as a plasmid preparation, from the recovered strain is labeled with a detectable agent, such as radioactive or fluorescent moiety, and placed in contact with the nucleic acid array under conditions which permit the labeled nucleic acid to hybridize to complementary nucleic acids on the array. The location on the array to which the labeled nucleic acids hybridize is determined to identify the gene which was overexpressed in the recovered strain. If desired the hybridized nucleic acids from a culture which was contacted with the compound may be compared to the hybridized nucleic acids from a control culture which was not contacted with the compound. Alternatively, the hybridized nucleic acids from a culture which was contacted with the compound may be directly identified without comparison to nucleic acids from a control culture.

In some instances, more than one strain may proliferate more rapidly in the presence of the compound. This may result from a variety of causes. For example, the concentration of the compound may not have been high enough to restrict proliferation only to cells which overexpress one gene product (i.e. the target gene product). While strains which overexpress the target gene product will be the most prevalent strain in the culture, other strains may also have proliferated. In such instances, the identity of the gene product in the strain which is most prevalent in the culture may be identified by quantitating the levels of each of the genes encoding proliferation-required proteins in the culture. This may be accomplished by quantitative PCR, DNA sequencing, hybridization, or array technology as described above.

In other instances, multiple strains will exhibit more rapid proliferation in the culture as a result of a common functional attribute. For example, the strains which proliferate more rapidly may each overexpress a gene product with a common enzymatic activity, such as serine protease activity for example. Alternatively, the strains which proliferate more rapidly may each overexpress a gene product with a common functional domain, such as a cAMP binding domain. In such instances, the common attribute of the strains which proliferate more rapidly may provide information as to the mode of action of the compound or the biochemical activity of the target of the compound. For example, if all of the overexpressed genes in the strains which proliferated more rapidly are serine proteases, the compound acts by inhibiting serine protease activity and the target protein is a serine protease. If desired, the compound may be derivatized and the efficacy of the derivatized compound against each of the strains which proliferated more rapidly may be assessed as described herein in order to identify derivatives which are capable of interacting with a wide range of targets sharing a common activity or binding site (i.e. derivatives which have a greater ability to inhibit the proliferation of all the strains than the original compound) or to identify derivatives having greater specificity for a desired target (i.e. derivatives which have a greater specificity for one of the strains than the original compound). For example, it is possible that a nonessential gene product expressed in the cell might also bind to the initial test compound in addition to the gene product required for proliferation. In such an instance, it is desirable to obtain a derivative of the initial test compound which is specific for the gene product required for proliferation. In addition, it is possible that two gene products required for proliferation might bind to the initial test compound but specificity for one of the gene products is desired.

Rather than employing a single culture which contains multiple strains each of which overexpresses a proliferation-required gene product described herein, the methods of the present invention may be performed using an array of individual strains (i.e. a collection of strains) each of which overexpresses a different proliferation-required gene product. For example, individual strains each overexpressing a different proliferation-required gene product may be grown in different wells of a multiwell plate. Each well is contacted with the compound (and, where appropriate an agent which regulates the level of expression from the promoter). The level of proliferation of the strains in each of the wells is determined to identify a strain which proliferated

more rapidly. The identity of the overexpressed gene product in the strain that proliferated more rapidly is determined as described above.

In another embodiment, individual strains each overexpressing a different proliferation-required gene product (i.e. a collection of strains) are grown at different locations on a solid medium, such as an agar plate. The medium contains the compound and where appropriate an agent which regulates the level of expression from the promoter). The level of proliferation of each of the strains is determined to identify a strain which proliferated more rapidly. The identity of the overexpressed gene product in the strain that proliferated more rapidly is determined as described above.

The above methods may be used to prioritize compound development or to determine whether the compound has been previously identified or whether the target of the compound is the target of a previously identified drug. In particular, if the product is a natural product, it is advantageous to determine whether it has been previously identified prior to investing significant effort in developing it. Thus, in some embodiments of the present invention, the target of a partially purified or purified natural product or a compound produced by combinatorial chemistry is identified using the methods described above and compared to the targets of known drugs. If the target is identical to that of a known drug, further development of the compound is halted.

Alternatively, an array of strains each of which overexpresses a different gene product described herein (i.e. a collection of strains) is grown on solid medium containing a compound to be evaluated. The location of each strain in the array and the gene product overexpressed by that strain is known. The pattern of colonies which grow in the presence of the compound is evaluated and compared to the pattern of colonies which grow in the presence of previously identified drugs. If the pattern of colonies which grow in the presence of the compound being evaluated is the same as the pattern of colonies which grow in the presence of a previously identified drug, further development of the compound is halted.

Additionally in some embodiments, the sequence of the gene product in a strain which proliferated more rapidly in the assays described above is compared to the sequence of gene products from heterologous organisms to determine the likely spectrum of species whose growth would be inhibited by the compound. If the gene product has a high degree of homology to gene products from heterologous species, it is likely that the compound would also inhibit the growth of these heterologous species. Homology may be determined using any of a variety of methods familiar to those skilled in the art. For example, homology may be determined using a computer program such as BLASTP or FASTA. The ability of the compound to inhibit the growth of the heterologous species may then be confirmed by comparing the growth of cells of the heterologous species in the presence and absence of the compound.

Current methods for identifying the target of compounds which inhibit cellular proliferation are laborious and time consuming. The above methods may be employed to allow the targets of a large number of compounds to be rapidly identified. In such methods, the methods described above

are simultaneously performed for each of a large number of compounds. For example, the compounds may be members of a library of compounds generated using combinatorial chemistry or members of a natural product library. In such methods, a plurality of cultures each comprising a plurality of strains each of which overexpresses a different gene product required for proliferation or a plurality of collections of individual strains each of which overexpresses a different gene product required for proliferation is obtained. Each culture or collection of strains is contacted with a different compound in the library and the target of the compound is identified as described above.

In another embodiment, the gene product described herein on which a compound which inhibits the proliferation of an organism acts is identified using a culture which comprises a mixture of strains of the organism including strains which underexpress a different gene product which is required for proliferation of the organism (i.e. at least some of the strains in the culture underexpress a gene product which is required for proliferation of the organism). Preferably, each of the strains in the culture underexpress a different a gene product which is required for the proliferation of the organism (i.e. all of the strains in the culture underexpress a gene product which is required for the proliferation of the organism). In some embodiments, the culture comprises at least one strain which underexpresses a gene product selected from the group consisting of a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581, a gene product whose activity or level is inhibited by a homologous antisense nucleic acid, a gene product encoded by a homologous coding nucleic acid, and a gene product comprising a homologous polypeptide.

Strains underexpressing the proliferation-required gene products described herein may be obtained using the methods described above. The culture may comprise any number of strains. For example the culture may comprise at least two strains, at least 10 strains, at least 20 strains, at least 30, strains, at least 50 strains, at least 100 strains, at least 300 strains or more than 300 strains which underexpress a gene product required for proliferation. In some embodiments, the strains in the culture in aggregate may underexpress all or most of the gene products required for proliferation of the organism.

The culture is contacted with a compound which inhibits proliferation of the organism. The compound may be a candidate drug compound obtained from any source. For example, the compound may be a compound generated using combinatorial chemistry, a compound from a natural product library, or an impure or partially purified compound, such as a compound in a partially purified natural extract. The culture is contacted with a sufficient concentration of the compound to inhibit the proliferation of strains of the organism in the culture which underexpress the gene product on which the compound acts, such that strains which do not underexpress the gene product on which the compound acts proliferate more rapidly in the culture than strains which do

underexpress said gene product on which said compound acts. Thus, after a sufficient period of time, the strain which underexpresses the gene product on which the compound acts will be less prevalent in the culture than strains which do not underexpress the gene product on which the compound acts. In one embodiment, the growth conditions and incubation period are selected so that only one strain, the strain underexpressing the target of the compound, proliferates at a reduced rate in the culture. In another embodiment, the growth conditions may be selected so that the strain underexpressing the target of the compound is not recovered from the culture. Thus, in one embodiment, a plurality of cultures containing a plurality of strains each of which underexpresses a different proliferation-required gene product may be grown in the presence of varying concentrations of the compound. In addition to varying the compound concentrations, in embodiments where expression of the proliferation-required gene product is under the control of a regulatable promoter, the plurality of cultures may be grown at varying concentrations of an agent which regulates the level of expression from the promoter, such as an inducer or an agent which reduces the effect of a repressor on transcription from the promoter. It will be appreciated, that the cultures may be grown in liquid medium in the presence of the compound whose target is to be identified (and where appropriate in the presence of an agent which regulates the level of expression from the promoter) or alternatively, a liquid culture comprising the strains which underexpress the proliferation-required gene products may be grown in the absence of the compound whose target is to be identified and then introduced onto a solid medium containing the compound (and, where appropriate, also containing an agent which regulates the level of expression from the promoter).

The identity of the underexpressed gene product which is the target of the compound may be determined using a variety of methods. For example, in some embodiments of the present invention, the nucleic acids present in the culture or collection of strains which was contacted with the compound may be compared to the nucleic acids present in a control culture or collection of strains which was not contacted with the compound to identify nucleic acids which are underrepresented in the culture or collection of strains contacted with the test compound relative to the control culture or strains. Alternatively, in some embodiments, the nucleic acids present in a culture or collection of strains contacted with the test compound may be analyzed to identify those nucleic acids which are missing or present at reduced levels without comparison to a control culture or collection of strains.

In some embodiments of the present invention, the strains which proliferated more slowly in the culture or collection of strains, i.e. strains having an decreased ability to proliferate in the presence of a test compound or which do not proliferate in the presence of a test compound, are identified as follows. Amplification products which are correlated with each of the underexpressed genes and which are distinguishable from one another are obtained from a culture or collection grown in the presence of a test compound. The amplification products are distinguished from one another to determine whether a particular amplification product is underrepresented in the culture or collection of strains. In some embodiments, the amplification products corresponding to each of the

gene products have lengths which permit them to be distinguished from one another. In another embodiment, one or more of the amplification products have similar or identical lengths but are distinguishable from one another based on a detectable agent, such as a dye, attached thereto. In some embodiments, amplification products which are underrepresented are identified by comparing the amplification products from the culture or collection of strains which was contacted with the test compound to the amplification products from a culture or collection of strains which was not contacted with the test compound. Alternatively, amplification products which are underrepresented in the culture or collection of strains may be identified simply by determining which amplification products are missing or present at reduced levels in the culture or collection of strains. The above methods for generating distinguishable amplification products may be used in conjunction with any of the methods for generating strains which underexpress gene products required for proliferation described herein in order to facilitate the identification of strains which proliferate more slowly in the presence of a test compound.

For example, in some embodiments of the present invention, each of the native promoters of each of the genes encoding gene product required for proliferation are replaced by a single desired replacement promoter. After growth of the culture or collection of strains containing the strains in which the promoters have been replaced in the presence of a test compound for a desired period of time, an amplification reaction is performed on nucleic acids obtained from the culture as follows.

The nucleic acids from the culture or collection of strains are divided into at least two aliquots. In a preferred embodiment the nucleic acids from the culture or collection of strains are divided into four aliquots. A single primer complementary to a nucleotide sequence within the replacement promoter , within the proliferation required genes, or within nucleic acid sequences adjacent to the promoter or proliferation required genes is divided into four groups Each group is labeled with a distinct detectable dye, such as the 6FAM™, TET™, VIC™, HEX™, NED™, and PET™ dyes obtainable from Applied Biosystems (Foster City, CA). For example, the DS-31 or DS-33 dye sets available from Applied Biosystems (Foster City, CA) may be used to label the primers. Each of the groups of labeled primers are added to each of the aliquots of the nucleic acids from the culture or collection of strains such that each aliquot of nucleic acid receives a single labeled primer with a single detectable dye thereon.

Each of the aliquots of nucleic acids also receives a set of unlabeled primers, with each of the unlabeled primers being complementary to a nucleotide sequence within the promoter, within a nucleotide sequence which is unique to one of the genes encoding gene products required for proliferation which were placed under the control of the replacement promoter, or within nucleotide sequences adjacent to the promoter or proliferation required genes. Each of the aliquots receives primers unique to 1/N proliferation required genes which were placed under the control of the replacement promoter, where N is the number of aliquots (i.e. if the culture or collection of strains consisted of 100 strains in which a gene required for proliferation was placed under the control of the replacement promoter and was divided into four aliquots, then each of the four aliquots of

nucleic acids from the culture or collection of strains would receive primers complementary to 25 of the genes). The unlabeled primers are selected so that each will yield an amplification product having a length distinguishable from the length of the amplification product produced with the other unlabeled primers. Preferably, the amplification products are between about 100-about 400 nucleotides in length, but any lengths which may be distinguished from each other may be used. In addition, in some of the embodiments some of the amplification products may have identical or very similar lengths but be distinguishable from one another due to labeling with distinguishable dyes.

A nucleic acid amplification reaction is conducted on each of the nucleic acid aliquots. The amplification products are then separated by length to identify amplification products decreased representation or which are absent in the culture or collection of strains. The amplification products are then correlated with the corresponding genes to determine which strains proliferated more slowly in the culture or collection of strains. If desired, amplification products having decreased representation in the culture may be identified by comparing the amplification products obtained from a culture or collection of strains which was contacted with the compound to amplification products obtained from a control culture or collection of strains which was not contacted with the compound. Alternatively, if desired, the amplification products which are missing or present at reduced levels in a culture which was contacted with the compound may be directly identified without comparison to a control culture which was not contacted with the compound.

For example, in some embodiments, the amplification products from each of the nucleic acid aliquots are pooled and subjected to capillary electrophoresis. The amplification products are detected by detecting the fluorescent dyes attached thereto and their lengths are determined to identify those amplification products having decreased representation in the culture or collection of strains. Figures 2A and 2B illustrate one embodiment of this method in which the absence of an amplification product from an amplification reaction performed on a culture comprising a plurality of strains underexpressing genes required for proliferation indicates that a test compound acts on the gene corresponding to the missing amplification product.

Alternatively, in another embodiment, a first amplification reaction is performed on nucleic acids obtained from a culture or collection of strains which was contacted with the compound using a first primer complementary to a nucleotide sequence present upstream or downstream of all of the overexpressed genes (such as a primer complementary to a nucleotide sequence in a replacement promoter upstream of all of the overexpressed genes) and a set of primers complementary to a nucleotide sequence unique to each of the strains (such as a primer complementary to a nucleotide sequence within each of the proliferation-required genes). One of the two amplification primers for each of the proliferation required genes is labeled with a dye as described above. Preferably, the common primer complementary to a nucleotide sequence upstream or downstream of all of the overexpressed genes is labeled with the dye. The primers used in the amplification reaction are designed so that the amplification product corresponding to each proliferation-required gene has a

unique length. A second amplification reaction is conducted on a control culture or collection of strains which was not contacted with the compound using the same primers as in the first amplification reaction. The amplification products from the first amplification reaction are compared to those from the second amplification reaction to identify one or more amplification products which are underrepresented in the culture or collection of strains. For example, the amplification products from the first amplification reaction may be run in a separate lane of a polyacrylamide gel or a separate capillary than the amplification products from the second amplification reaction and the two lanes or capillaries are compared to one another.

Alternatively, in some embodiments, the primers in the second amplification reaction are labeled with a different dye which is distinguishable from the dye used in the first amplification reaction. In this embodiment, the amplification reactions may be pooled and run in the same lane on a polyacrylamide gel or in the same capillary and the products from each amplification reaction are compared by comparing the amount of each dye present for each amplification product. Figures 3A and 3B illustrate one embodiment of this method in which the absence of an amplification product from the amplification reaction performed on a culture comprising a plurality of strains underexpressing genes required for proliferation which was contacted with the compound indicates that a test compound acts on the gene corresponding to the missing amplification product.

If desired, rather than dividing the culture into aliquots, individual amplification reactions may be conducted on nucleic acids obtained from the culture or collection of strains. Each amplification reaction contains primers which will yield an amplification product specific for only one of the proliferation required genes. The resulting amplification products from each of the individual amplification reactions are pooled and amplification products having decreased representation in the culture are identified as described above.

In an alternative embodiment, the representation of each strain in the culture may be assessed by hybridizing detectably labeled nucleic acids encoding the proliferation-required gene products, or portions thereof, obtained from the culture to an array comprising nucleic acids encoding the gene products required for proliferation or portions thereof. Each nucleic acid encoding a gene product required for proliferation or portion thereof occupies a known location on the array. The signal from each location on the array is quantitated to identify those nucleic acids encoding a proliferation-required gene product which are underrepresented in the culture. If desired the hybridized nucleic acids from a culture which was contacted with the compound may be compared to the hybridized nucleic acids from a control culture which was not contacted with the compound. Alternatively, the hybridized nucleic acids from a culture which was contacted with the compound may be directly analyzed without comparison to nucleic acids from a control culture.

In another alternative, each strain underexpressing a gene product required for proliferation may be constructed to contain a unique nucleic acid sequence (referred to herein as a "tag"). The tag may be included in the chromosome of each strain or in an extrachromosomal vector. For example, the tag could be included in a vector encoding an antisense nucleic acid complementary to

a gene encoding a gene product required for proliferation or a portion of such a gene or the tag may be included in the antisense nucleic acid itself. The representation of each strain in the culture may be assessed by performing an amplification reaction using primers complementary to each of the tags and quantitating the levels of the resulting amplification products to identify a tag which is underrepresented or absent from the culture. Since each tag corresponds to one strain, the strain which is underrepresented or absent from the culture may be identified. If desired the tags present in a culture which was contacted with the compound may be compared to the tags present in a control culture which was not contacted with the compound. Alternatively, the tags present in a culture which was contacted with the compound may be analyzed without comparison to a control culture.

It will be appreciated that, if desired, unique tags may also be used in embodiments in which gene products required for proliferation are overexpressed. In some aspects of such embodiments, the tags may be within or adjacent to the promoter which drives expression of the gene encoding the gene product. In such embodiments, the gene product which is overexpressed in strains which proliferate more rapidly in the culture may be identified by detecting the presence or amount of the unique tag corresponding to that gene product in the culture.

In some instances, more than one strain may proliferate less rapidly in the presence of the compound. This may result from a variety of causes. For example, the concentration of the compound may not have been high enough to reduce the proliferation only in cells which underexpress one gene product (i.e. the target gene product). While strains which underexpress the target gene product will be the least prevalent strain in the culture, other strains may also be underrepresented. In such instances, the identity of the gene product in the strain which is least prevalent in the culture (or not recovered from the culture) may be identified by quantitating the levels of each of the genes encoding proliferation-required proteins in the culture. This may be accomplished by quantitative PCR, DNA sequencing, hybridization, or array technology as described above.

In other instances, multiple strains will exhibit less rapid proliferation in the culture as a result of a common functional attribute. For example, the strains which proliferate less rapidly (or the strains which are not recovered from the culture) may each underexpress a gene product with a common enzymatic activity, such as serine protease activity for example. Alternatively, the strains which proliferate less rapidly (or the strains which are not recovered from the culture) may each underexpress a gene product with a common functional domain, such as a cAMP binding domain. In such instances, the common attribute of the strains which proliferate less rapidly (or the strains which are not recovered from the culture) may provide information as to the mode of action of the compound or the biochemical activity of the target of the compound. For example, if all of the underexpressed genes in the strains which proliferated less rapidly are serine proteases, the compound acts by inhibiting serine protease activity and the target protein is a serine protease. If desired, the compound may be derivatized and the efficacy of the derivatized compound against

each of the strains which proliferated more rapidly may be assessed as described herein in order to identify derivatives which are capable of interacting with a wide range of targets sharing a common activity or binding site (i.e. derivatives which have a greater ability to inhibit the proliferation of all the strains than the original compound) or to identify derivatives having greater specificity for a desired target (i.e. derivatives which have a greater specificity for one of the strains than the original compound).

Rather than employing a single culture which contains multiple strains each of which underexpresses a proliferation-required gene product described herein, the methods of the present invention may be performed using an array of individual strains (i.e. a collection of strains) each of which underexpresses a different proliferation-required gene product. For example, individual strains each underexpressing a different proliferation-required gene product may be grown in different wells of a multiwell plate. Each well is contacted with the compound (and, where appropriate an agent which regulates the level of expression from the promoter). The level of proliferation of the strains in each of the wells is determined to identify a strain which proliferated less rapidly or which did not proliferate at all. The identity of the underexpressed gene product in the strain that proliferated less rapidly or which did not proliferate at all is determined as described above.

In another embodiment, individual strains each underexpressing a different proliferation-required gene product (i.e. a collection of strains) are grown at different locations on a solid medium, such as an agar plate. The medium contains the compound and, where appropriate, an agent which regulates the level of expression from the promoter. The level of proliferation of each of the strains is determined to identify a strain which proliferated less rapidly (or a strain which is not recovered from the culture). The identity of the underexpressed gene product in the strain that proliferated less rapidly (or the strain which is not recovered from the culture) is determined as described above.

The above methods may be used to prioritize compound development or to determine whether the compound has been previously identified or whether the target of the compound is the target of a previously identified drug. In particular, if the product is a natural product is advantageous to determine whether it has been previously identified prior to investing significant effort in developing it. Thus, in some embodiments of the present invention, the target of a partially purified or purified natural product or a compound produced by combinatorial chemistry is identified using the methods described above and compared to the targets of known drugs. If the target is identical to that of a known drug, further development of the compound is halted.

Alternatively, an array of strains each of which underexpresses a different gene product described herein (i.e. a collection of strains) is grown on solid medium containing a compound to be evaluated. The location of each strain in the array and the gene product underexpressed by that strain is known. The pattern of colonies which grow less rapidly or fail to grow in the presence of the compound is evaluated and compared to the pattern of colonies which grow less rapidly or fail

to grow in the presence of previously identified drugs. If the pattern of colonies which grow less rapidly or fail to grow in the presence of the compound being evaluated is the same as the pattern of colonies which grow less rapidly or fail to grow in the presence of a previously identified drug, further development of the compound is halted.

Additionally, the nucleotide sequence of the gene product described herein in a strain which proliferated less rapidly (or a strain which was not recovered from the culture) in the assays described above is compared to the nucleotide sequence of gene products from heterologous organisms to determine the likely spectrum of species whose growth would be inhibited by the compound. If the gene product has a high degree of homology to gene products from heterologous species, it is likely that the compound would also inhibit the growth of these heterologous species. Homology may be determined using any of a variety of methods familiar to those skilled in the art. For example, homology may be determined using a computer program such as BLASTP or FASTA. The ability of the compound to inhibit the growth of the heterologous species may then be confirmed by comparing the growth of cells of the heterologous species in the presence and absence of the compound.

In other embodiments, the present invention uses collections or cultures of strains comprising both strains which overexpress gene products described herein required for cellular proliferation and strains which underexpress the same gene products required for cellular proliferation. The gene product which is overexpressed or underexpressed in each strain may be a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581, a gene product whose activity or level is inhibited by a homologous antisense nucleic acid, a gene product encoded by a homologous coding nucleic acid, and a gene product comprising a homologous polypeptide.

The culture or collection of strains is contacted with a compound and the nucleic acids present in the culture or collection of strains are analyzed. Preferably, nucleic acids derived from overexpressing strains can be distinguished from those derived from underexpressing strains. For example, the overexpressing strains may be obtained using promoter replacement as described above while the underexpressing strains may be obtained by expressing antisense nucleic acids. Accordingly, in one embodiment, amplification primers may be designed which will uniquely amplify nucleic acids from the overexpressing strains or the underexpressing strains. If a compound acts on a gene product which was overexpressed and underexpressed in the culture, then the amplification product obtained from the strain in the culture or collection which overexpressed gene product will be overrepresented in the culture or collection while the amplification product obtained from the strain which underexpressed the gene product will be underrepresented in the culture or collection. If desired, nucleic acids from a culture or collection which was contacted with

the compound may be compared to nucleic acids from a control culture or collection which was not contacted with the compound. Alternatively, nucleic acids from a culture or collection which was contacted with the compound may be directly analyzed without comparison to a control culture or collection.

In some embodiments, strains are constructed in which a nucleic acid complementary to a gene encoding a gene product described herein required for proliferation or a portion thereof is operably linked to a regulatable promoter. For example, in some embodiments, the strains may transcribe an antisense nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 or fragments thereof which inhibit proliferation or reduce the activity or level of the gene product encoded by the gene comprising a nucleotide sequence complementary to the antisense nucleic acid or homologous antisense nucleic acids or fragments thereof. In other embodiments, the strains may transcribe an antisense nucleic acid which reduces the activity or level of a gene product encoded by SEQ ID NOs.: 6214-42397, the polypeptides of SEQ ID NOs.: 42398-78581, homologous coding nucleic acids or homologous polypeptides. A culture comprising a plurality of such strains wherein each strain expresses an antisense nucleic acid against a different gene product required for proliferation is grown in the presence of varying levels of a compound which inhibits proliferation and in the presence of varying levels of an agent which regulates the level of transcription from the regulatable promoter. Nucleic acids samples are obtained from the culture, detectably labeled and hybridized to a solid support comprising nucleic acids containing the genes encoding the proliferation-required gene products or a portion thereof. The level of hybridization is quantitated for each nucleic acid encoding each of the proliferation-required gene products to determine the rate at which each of the strains proliferated in the culture. If the antisense nucleic acid expressed by a strain in the culture is not complementary to all or a portion of the gene encoding the target of the compound (i.e. a nonspecific strain), then the hybridization intensity for that strain will not be correlated with the concentration of the compound (See Figure 4), while if the antisense nucleic acid expressed by a strain in the culture is complementary to all or a portion of the gene encoding the target of the compound, the hybridization intensity for that strain will be intimately correlated with the concentration of the compound (See Figure 5). In this manner, the target of the compound may be identified. It will be appreciated that, as described above, rather than growing the strains in a single culture, each strain may be grown in a different location on a solid medium or in a different well of a multiwell plate.

The methods described above can be simultaneously performed for each of a large number of compounds. For example, the compounds may be members of a library of compounds generated using combinatorial chemistry or members of a natural product library. In such methods, a plurality of cultures each comprising a plurality of strains each of which overexpresses or underexpresses a different gene product required for proliferation or a plurality of collections of individual strains each of which overexpresses or underexpresses a different gene product required for proliferation is

obtained. Each culture or collection of strains is contacted with a different compound in the library and the target of the compound is identified as described above.

In still another embodiment, the antisense nucleic acids of the present invention (including the antisense nucelic acids of SEQ ID NOs. 1-6213 fragments thereof or homologous antisense nucleic acids or fragements thereof) that inhibit bacterial growth or proliferation can be used as antisense therapeutics for killing bacteria. The antisense sequences can be complementary to one of SEQ ID NOs.: 6214-42397 or fragments thereof, homologous coding nucleic acids or fragments thereof. Alternatively, antisense therapeutics can be complementary to operons in which proliferation-required genes reside (i.e. the antisense nucleic acid may hybridize to a nucleotide sequence of any gene in the operon in which the proliferation-required genes reside). Further, antisense therapeutics can be complementary to a proliferation-required gene or portion thereof with or without adjacent noncoding sequences, an intragenic sequence (i.e. a sequence within a gene), an intergenic sequence (i.e. a sequence between genes), a sequence spanning at least a portion of two or more genes, a 5' noncoding region or a 3' noncoding region located upstream or downstream from the actual sequence that is required for bacterial proliferation or an operon containing a proliferation-required gene.

In addition to therapeutic applications, the present invention encompasses the use of nucleic acids complementary to nucleic acids required for proliferation as diagnostic tools. For example, nucleic acid probes comprising nucleotide sequences complementary to proliferation-required sequences that are specific for particular species of cells or microorganisms can be used as probes to identify particular microorganism species or cells in clinical specimens. This utility provides a rapid and dependable method by which to identify the causative agent or agents of a bacterial infection. This utility would provide clinicians the ability to accurately identify the species responsible for the infection and amdminister a compound effective against it. In an extension of this utility, antibodies generated against proteins translated from mRNA transcribed from proliferation-required sequences can also be used to screen for specific cells or microorganisms that produce such proteins in a species-specific manner.

Other embodiments of the present invention include methods of identifying compounds which inhibit the activity of gene products required for cellular proliferation using rational drug design. As discussed in more detail below, in such methods, the structure of the gene product is determined using techniques such as x-ray crystallography or computer modeling. Compounds are screened to identify those which have a structure which would allow them to interact with the gene product or a portion thereof to inhibit its activity. The compounds may be obtained using any of a variety of methods familiar to those skilled in the art, including combinatorial chemistry. In some embodiments, the compounds may be obtained from a natural product library. In some embodiments, compounds having a structure which allows them to interact with the active site of a gene product, such as the active site of an enzyme, or with a portion of the gene product which interacts with another biomolecule to form a complex are identified. If desired, lead compounds may be identified and further optimized to provide compounds which are highly effective against the gene product.

The following examples teach the genes of the present invention and a subset of uses for the genes identified as required for proliferation. These examples are illustrative only and are not intended to limit the scope of the present invention.

EXAMPLES

The following examples are directed to the identification and exploitation of genes required for proliferation. Methods of gene identification are discussed as well as a variety of methods to utilize the identified sequences. It will be appreciated that any of the antisense nucleic acids, proliferartion-required genes or proliferation-required gene products described herein, or portions thereof, may be used in the procedures described below, including the antisense nucleic acids of SEQ ID NOs.: 1-6213, the nucleic acids of SEQ ID NOS.: 6214-42397, or the polypeptides of SEQ ID NOs.: 42398-78581. Likewise, homologous antisense nucleic acids, homologous coding nucleic acids, homologous polypeptides or portions of any of the above-mentioned nucleic acids or polypeptides, may be used in any of the procedures described below.

Genes Identified as Required for Proliferation of *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Salmonella typhimurium*.

Genomic fragments were operably linked to an inducible promoter in a vector and assayed for growth inhibition activity. Example 1 describes the examination of a library of genomic fragments cloned into vectors comprising inducible promoters. Upon induction with xylose or IPTG, the vectors produced an RNA molecule corresponding to the subcloned genomic fragments. In those instances where the genomic fragments were in an antisense orientation with respect to the promoter, the transcript produced was complementary to at least a portion of an mRNA (messenger RNA) encoding a *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa* or *Salmonella typhimurium* gene product such that they interacted with sense mRNA produced from various *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa* or *Salmonella typhimurium* genes and thereby decreased the translation efficiency or the level of the sense messenger RNA thus decreasing production of the protein encoded by these sense mRNA molecules. In cases where the sense mRNA encoded a protein required for proliferation, bacterial cells containing a vector from which transcription from the promoter had been induced failed to grow or grew at a substantially reduced rate. Additionally, in cases where the transcript produced was complementary to at least a portion of a non-translated RNA and where that non-translated RNA was required for proliferation, bacterial cells containing a vector from which transcription from the promoter had been induced also failed to grow or grew at a substantially reduced rate. In contrast, cells grown under non-inducing conditions grow at a normal rate.

The above method was used to identify genes required for cellular proliferation in *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Salmonella typhimurium*. Additionally, a number of genes required for cellular

proliferation in *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Salmonella typhimurium*, which have been described in the following U.S. Patent Applications: U.S. Patent Application Serial Number 09/492,709, filed January 27, 2000; U.S. Patent Application Serial Number 09/711,164, filed November 9, 2000; U.S. Patent Application Serial Number 09/741,669, filed December 19, 2000 and U.S. Patent Application Serial Number 09/815,242 filed March 21, 2001, U.S. Provisional Patent Application Serial Number 60/342,923, filed October 25, 2001, have been previously identified using the above method.

EXAMPLE 1

Inhibition of Bacterial Proliferation after Induction of Antisense Expression

To identify genes required for proliferation of *E. coli*, random genomic fragments were cloned into the IPTG-inducible expression vector pLEX5BA (Krause et al., J. Mol. Biol. 274: 365 (1997) or a modified version of pLEX5BA, pLEX5BA-3' in which a synthetic linker containing a T7 terminator was ligated between the PstI and HindIII sites of pLEX5BA. In particular, to construct pLEX5BA-3', the following oligonucleotides were annealed and inserted into the PstI and HindIII sites of pLEX5BA:

5'-GTCTAGCATAACCCCTTGGGGCCTCTAAACGGGTCCTTGAGGGGTTTTTTGA-3' (SEQ ID NO: 78584)

5'-AGCTTCAAAAAACCCCTCAAGGACCCGTTTAGAGGCCCCAAGGGGTTAT GCTAGACTGCA-3' (SEQ ID NO: 78585)

Random fragments of *E. coli* genomic DNA were generated by DNAseI digestion or sonication, filled in with T4 polymerase, and cloned into the SmaI site of pLEX5BA or pLEX5BA-3'. Upon activation or induction, the promoter transcribed the random genomic fragments.

A number of vectors which allow the production of transcripts which have an extended lifetime in *E. coli* as well as other Gram negative bacteria can also be utilized in conjunction with these antisense inhibition experiments. Such vectors are described in U.S. Provisional Patent Application Serial Number 60/343,512, filed December 21, 2001. Briefly, the stabilized antisense RNA may comprise an antisense RNA which was identified as inhibiting proliferation as described above which has been engineered to contain at least one stem loop flanking each end of the antisense nucleic acid. In some embodiments, the at least one stem-loop structure formed at the 5' end of the stabilized antisense nucleic acid comprises a flush, double stranded 5' end. In some embodiments, one or more of the stem loops comprises a rho independent terminator. In additional embodiments, the stabilized antisense RNA lacks a ribosome binding site. In further embodiments, the stabilized RNA lacks sites which are cleaved by one or more RNAses, such as RNAse E or RNAse III. In some embodiments, the stabilized antisense RNA may be transcribed in a cell which the activity of at least one enzyme involved in RNA degradation has been reduced. For example, the activity of an enzyme such as RNase E, RNase II, RNase III, polynucleotide phosphorylase, and poly(A) polymerase, RNA helicase, enolase or an enzyme having similar functions may be reduced in the cell.

To study the effects of transcriptional induction in liquid medium, growth curves were carried out by back diluting cultures 1:200 into fresh media with or without 1 mM IPTG and measuring the OD_{450} every 30 minutes (min). To study the effects of transcriptional induction on solid medium, 10^2, 10^3, 10^4, 10^5, 10^6, 10^7 and 10^8 fold dilutions of overnight cultures were prepared. Aliquots of from 0.5 to 3 µl of these dilutions were spotted on selective agar plates with or without 1 mM IPTG. After overnight incubation, the plates were compared to assess the sensitivity of the clones to IPTG.

Of the numerous clones tested, some clones were identified as containing a sequence that inhibited *E. coli* growth after IPTG induction. Accordingly, the gene to which the inserted nucleic acid sequence corresponds, or a gene within the operon containing the inserted nucleic acid, is required for proliferation in *E. coli*.

Nucleic acids involved in proliferation of *Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Salmonella typhimurium* were identified as follows. Randomly generated fragments of *Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa* or *Salmonella typhimurium* genomic DNA were transcribed from inducible promoters.

In the case of *Staphylococcus aureus,* a novel inducible promoter system, XylT5, comprising a modified T5 promoter fused to the *xylO* operater from the *xylA* promoter of *Staphylococcus aureus* was used. The promoter is described in U.S. Patent Application Serial Number 10/032,393, filed December 21, 2001. Transcription from this hybrid promoter is inducible by xylose.

Randomly generated fragments of *Salmonella typhimurium* genomic DNA were transcribed from an IPTG inducible promoter in pLEX5BA (Krause et al., J. Mol. Biol. 274: 365 (1997) or a derivative thereof. Randomly generated fragements of *Klebsiella pneumoniae* genomic DNA were expressed from an IPTG inducible promoter in pLEX5BA-Kan. To construct pLEX5BA-kan, pLEX5BA was digested to completion with *ClaI* in order to remove the *bla* gene. Then the plasmid was treated with a partial *NotI* digestion and blunted with T4 DNA polymerase. A 3.2 kbp fragment was then gel purified and ligated to a blunted 1.3 kbp kan gene from pKanπ. Kan resistant transformants were selected on Kan plates. Orientation of the kan gene was checked by *SmaI* digestion. A clone, which had the kan gene in the same orientation as the bla gene, was used to identify genes required for proliferation of *Klebsiella pneumoniae.* Randomly generated fragments of *Pseudomonas aeruginosa* genomic DNA were trancribed from a two-component inducible promoter system. Integrated on the chromosome was the T7 RNA polymerase gene regulated by *lac*UV5/ *lac*O (Brunschwig, E. and Darzins, A. 1992. Gene 111:35-41. On a separate plasmid, a T7 gene 10 promoter, which is transcribed by T7 RNA polymerase, was fused with a *lac*O operator followed by a multiple cloning site.

Should the genomic DNA downstream of the promoter contain, in an antisense orientation, at least a portion of an mRNA or a non-translated RNA encoding a gene product involved in proliferation, then induction of transcription from the promoter will result in detectable inhibition of proliferation.

In the case of *Staphylococcus aureus*, a shotgun library of *Staphylococcus aureus* genomic fragments was cloned into the vector pXylT5-P15a, which harbors the XylT5 inducible promoter. The vector was linearized at a unique *Bam*HI site immediately downstream of the XylT5 promoter/operator. The linearized vector was treated with shrimp alkaline phosphatase to prevent reclosure of the linearized ends. Genomic DNA isolated from *Staphylococcus aureus* strain RN450 was fully digested with the restriction enzyme *Sau*3A , or , alternatively, partially digested with DNase I and "blunt-ended" by incubating with T4 DNA polymerase. Random genomic fragments between 200 and 800 base pairs in length were selected by gel purification. The size-selected genomic fragments were added to the linearized and dephosphorylated vector at a molar ratio of 0.1 to 1, and ligated to form a shotgun library.

The ligated products were transformed into electrocompetent *E. coli* strain XL1-Blue MRF' (Stratagene) and plated on LB medium with supplemented with carbenicillin at 100 μg/ml. Resulting colonies numbering 5 x 10^5 or greater were scraped and combined, and were then subjected to plasmid purification.

The purified library was then transformed into electrocompetent *Staphylococcus aureus* RN4220. Resulting transformants were plated on agar containing LB + 0.2% glucose (LBG medium) + chloramphenicol at 15 μg/ml (LBG+CM15 medium) in order to generate 100 to 150 platings at 500 colonies per plating. The colonies were subjected to robotic picking and arrayed into wells of 384 well culture dishes. Each well contained 100μl of LBG + CM15 liquid medium. Inoculated 384 well dishes were incubated 16 hours at 37°C, and each well was robotically gridded onto solid LBG + CM15 medium with or without 2% xylose. Gridded plates were incubated 16 hours at 37°C, and then manually scored for arrayed colonies that were growth-compromised in the presence of xylose.

Arrayed colonies that were growth-sensitive on medium containing 2% xylose, yet were able to grow on similar medium lacking xylose, were subjected to further growth sensitivity analysis as follows: Colonies from the plate lacking xylose were manually picked and inoculated into individual wells of a 96 well culture dish containing LBG + CM15, and were incubated for 16 hours at 37°C. These cultures were robotically diluted 1/100 into fresh medium and allowed to incubate for 4 hours at 37°C, after which they were subjected to serial dilutions in a 384 well array and then gridded onto media containing 2% xylose or media lacking xylose. After growth for 16 hours at 37°C, the arrays that resulted on the two media were compared to each other. Clones that grew similarly at all dilutions on both media were scored as a negative and were no longer considered. Clones that grew on xylose medium but failed to grow at the same serial dilution on the non-xylose plate were given a score based on the differential, i.e. should the clone grow at a

serial dilution of 10^4 or less on the xylose plate and grow at a serial dilution of 10^8 or less on the non-xylose plate, then the corresponding clone received a score of "4" representing the log difference in growth observed.

For *Salmonella typhimurium* and *Klebsiella pneumoniae* growth curves were carried out by back diluting cultures 1:200 into fresh media containing 1 mM IPTG or media lacking IPTG and measuring the OD_{450} every 30 minutes (min). To study the effects of transcriptional induction on solid medium, 10^2, 10^3, 10^4, 10^5, 10^6, 10^7 and 10^8 fold dilutions of overnight cultures were prepared. Aliquots of from 0.5 to 3 µl of these dilutions were spotted on selective agar plates with or without 1 mM IPTG. After overnight incubation, the plates were compared to assess the sensitivity of the clones to IPTG.

Nucleic acids involved in proliferation of *Pseudomonas aeruginosa* were identified as follows. Randomly generated fragments of *Pseudomonas aeruginosa* genomic DNA were transcribed from a two-component inducible promoter system. Integrated on the chromosome was the T7 RNA polymerase gene regulated by *lac*UV5/ *lac*O (Brunschwig, E. and Darzins, A. 1992. Gene 111:35-41). On an expression plasmid there was a T7 gene 10 promoter, which is transcribed by T7 RNA polymerase, fused with a *lac*O operator followed by a multiple cloning site. Transcription from this hybrid promoter is inducible by IPTG. Should the genomic DNA downstream of the promoter contain, in an antisense orientation, at least a portion of an mRNA encoding a gene product involved in proliferation, then induction of expression from the promoter will result in detectable inhibition of proliferation.

A shotgun library of *Pseudomonas aeruginosa* genomic fragments was cloned into the vectors pEP5, pEP5S, or other similarly constructed vectors which harbor the T7*lac*O inducible promoter. The vector was linearized at a unique *Sma*I site immediately downstream of the T7*lac*O promoter/operator. The linearized vector was treated with shrimp alkaline phosphatase to prevent reclosure of the linearized ends. Genomic DNA isolated from *Pseudomonas aeruginosa* strain PAO1 was partially digested with DNase I and "blunt-ended" by incubating with T4 DNA polymerase. Random genomic fragments between 200 and 800 base pairs in length were selected by gel purification. The size-selected genomic fragments were added to the linearized and dephosphorylated vector at a molar ratio of 2 to 1, and ligated to form a shotgun library.

The ligated products were transformed into electrocompetent *E. coli* strain XL1-Blue MRF' (Stratagene) and plated on LB medium with carbenicillin at 100 µg/ml or Streptomycin 100 µg/ml. Resulting colonies numbering 5 x 10^5 or greater were scraped and combined, and were then subjected to plasmid purification.

The purified library was then transformed into electrocompetent *Pseudomonas aeruginosa* strain PAO1. Resulting transformants were plated on LB agar with carbenicillin at 100 µg/ml or Streptomycin 40 µg/ml in order to generate 100 to 150 platings at 500 colonies per plating. The colonies were subjected to robotic picking and arrayed into wells of 384 well culture dishes. Each well contained 100 µl of LB + CB 100 or Streptomycin 40 liquid medium. Inoculated 384 well

dishes were incubated 16 hours at room temperature, and each well was robotically gridded onto solid LB + CB100 or Streptomycin 40 medium with or without 1 mM IPTG. Gridded plates were incubated 16 hours at 37°C, and then manually scored for arrayed colonies that were growth-compromised in the presence of IPTG.

Arrayed colonies that were growth-sensitive on medium containing 1 mM IPTG, yet were able to grow on similar medium lacking IPTG, were subjected to further growth sensitivity analysis as follows: Colonies from the plate lacking IPTG were manually picked and inoculated into individual wells of a 96 well culture dish containing LB + CB100 or Streptomycin 40, and were incubated for 16 hours at 30°C. These cultures were robotically diluted 1/100 into fresh medium and allowed to incubate for 4 hours at 37°C, after which they were subjected to serial dilutions in a 384 well array and then gridded onto media with and without 1 mM IPTG. After growth for 16 hours at 37°C, the arrays of serially diluted spots that resulted were compared between the two media. Clones that grew similarly at all dilutions on both media were scored as a negative and were no longer considered. Clones that grew on IPTG medium but failed to grow at the same serial dilution on the non-IPTG plate were given a score based on the differential, i.e. should the clone grow at a serial dilution of 10^4 or less on the IPTG plate and grow at a serial dilution of 10^8 or less on the IPTG plate, then the corresponding clone received a score of "4" representing the log difference in growth observed.

Following the identification of those vectors that, upon induction, negatively impacted *Pseudomonas aeruginosa* growth or proliferation, the inserts or nucleic acid fragments contained in those vectors were isolated for subsequent characterization. Vectors of interest were subjected to nucleic acid sequence determination.

Nucleic acids involved in proliferation of *E. faecalis* were identified as follows. Randomly generated fragments of genomic DNA were expressed from the vectors pEPEF3 or pEPEF14, which contain the CP25 or P59 promoter, respectively, regulated by the xyl operator/repressor. These plasmids as well as other vectors useful for the expression of nucleic acids in *Enterococcus faecalis* and other Gram positive organisms are described in U.S. Patent Application Serial Number 10/032,393, filed December 21, 2001, the disclosure or which is incorportated herein by reference in its entirety. Should the genomic DNA downstream of the promoter contain, in an antisense orientation, at least a portion of a mRNA encoding a gene product involved in proliferation, then induction of expression from the promoter will result in detectable inhibition of proliferation.

A shotgun library of *E. faecalis* genomic fragments was cloned into the vector pEPEF3 or pEPEF14, which harbor xylose inducible promoters. The vector was linearized at a unique *Sma*I site immediately downstream of the promoter/operator. The linearized vector was treated with alkaline phosphatase to prevent reclosure of the linearized ends. Genomic DNA isolated from *E. faecalis* strain OG1RF was partially digested with DNase I and "blunt-ended" by incubating with T4 DNA polymerase. Random genomic fragments between 200 and 800 base pairs in length were

selected by gel purification. The size-selected genomic fragments were added to the linearized and dephosphorylated vector at a molar ratio of 2 to 1, and ligated to form a shotgun library.

The ligated products were transformed into electrocompetent *E. coli* strain TOP10 cells (Invitrogen) and plated on LB medium with erythromycin (Erm) at 150 μg/ml. Resulting colonies numbering 5 x 10^5 or greater were scraped and combined, and were then subjected to plasmid purification.

The purified library was then transformed into electrocompetent *E. faecalis* strain OG1RF. Resulting transformants were plated on Todd-Hewitt (TH) agar with erythromycin at 10 μg/ml in order to generate 100 to 150 platings at 500 colonies per plating. The colonies were subjected to robotic picking and arrayed into wells of 384 well culture dishes. Each well contained 100 μl of THB + Erm 10 μg/ml. Inoculated 384 well dishes were incubated 16 hours at room temperature, and each well was robotically gridded onto solid TH agar + Erm with or without 5% xylose. Gridded plates were incubated 16 hours at 37°C, and then manually scored for arrayed colonies that were growth-compromised in the presence of xylose.

Arrayed colonies that were growth-sensitive on medium containing 5% xylose, yet were able to grow on similar medium lacking xylose, were subjected to further growth sensitivity analysis. Colonies from the plate lacking xylose were manually picked and inoculated into individual wells of a 96 well culture dish containing THB + Erm 10, and were incubated for 16 hours at 30°C. These cultures were robotically diluted 1/100 into fresh medium and allowed to incubate for 4 hours at 37°C, after which they were subjected to serial dilution on plates containing 5% xylose or plates lacking xylose. After growth for 16 hours at 37°C, the arrays of serially diluted spots that resulted were compared between the two media. Colonies that grew similarly on both media were scored as a negative and corresponding colonies were no longer considered. Colonies on xylose medium that failed to grow to the same serial dilution compared to those on the non-xylose plate were given a score based on the differential. For example, colonies on xylose medium that only grow to a serial dilution of -4 while they were able to grow to -8 on the non-xylose plate, then the corresponding transformant colony received a score of "4" representing the log difference in growth observed.

Following the identification of those vectors that, upon induction, negatively impacted *E. faecalis* growth or proliferation, the inserts or nucleic acid fragments contained in those expression vectors were isolated for subsequent characterization. The inserts in the vectors of interest were subjected to nucleotide sequence determination.

It will be appreciated that other restriction enzymes and other endonucleases or methodologies may be used to generate random genomic fragments. In addition, random genomic fragments may be generated by mechanical shearing. Sonication and nebulization are two such techniques commonly used for mechanical shearing of DNA.

EXAMPLE 2

Nucleotide Sequence Determination of Identified Clones Transribing Nucleic Acid Fragments with Detrimental Effects on *Escherichia coli*, *Staphylococcus aureus*, *Enterococcus faecalis*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* or *Salmonella typhimurium* Proliferation

Plasmids from clones that received a dilution plating score of "2" or greater were isolated to obtain the genomic DNA insert responsible for growth inhibition as follows.

The nucleotide sequences of the nucleic acid sequences which inhibited the growth of *Escherichia coli* were determined using plasmid DNA isolated using QIAPREP (Qiagen, Valencia, CA) and methods supplied by the manufacturer. The primers used for sequencing the inserts were 5' - TGTTTATCAGACCGCTT - 3' (SEQ ID NO: 78586) and 5' - ACAATTTCACACAGCCTC - 3' (SEQ ID NO: 78587). These sequences flank the polylinker in pLEX5BA.

The nucleotide sequences of the nucleic acid sequences which inhibited the growth of *Staphylococcus aureus* were determined as follows. *Staphylococcus aureus* were grown in standard laboratory media (LB or TB with 15 ug/ml Chloramphenicol to select for the plasmid). Growth was carried out at 37°C overnight in culture tubes or 2 ml deep well microtiter plates.

Lysis of *Staphylococcus aureus* was performed as follows. Cultures (2-5 ml) were centrifuged and the cell pellets resuspended in 1.5 mg/ml solution of lysostaphin (20 µl/ml of original culture) followed by addition of 250 µl of resuspension buffer (Qiagen). Alternatively, cell pellets were resuspended directly in 250 µl of resuspension buffer (Qiagen) to which 5-20 µl of a 1 mg/ml lysostaphin solution were added.

DNA was isolated using Qiagen miniprep kits or Wizard (Qiagen) miniprep kits according to the instructions provided by the manufacturer.

The genomic DNA inserts were amplified from the purified plasmids by PCR as follows.

1 µl of Qiagen purified plasmid was put into a total reaction volume of 25 µl Qiagen Hot Start PCR mix. For *Staphylococcus aureus*, the following primers were used in the PCR reaction:

pXylT5F: CAGCAGTCTGAGTTATAAAATAG (SEQ ID NO: 78588)

LexL TGTTTTATCAGACCGCTT (SEQ ID NO: 78589)

Similar methods were conducted for *Salmonella typhimurium* and *Klebsiella pneumoniae*. For *Salmonella typhimurium* and *Klebsiella pneumoniae* the following primers were used:

5' - TGTTTTATCAGACCGCTT - 3' (SEQ ID NO: 78589) and

5'-ACAATTTCACACAGCCTC-3' (SEQ ID NO: 78587)

PCR was carried out in a PE GenAmp with the following cycle times:

Step 1. 95° C 15 min

Step 2. 94° C 45 sec

Step 3. 54° C 45 sec

Step 4. 72° C 1 minute

Step 5. Return to step 2, 29 times

Step 6. 72° C 10 minutes

Step 7. 4° C hold

The PCR products were cleaned using Qiagen Qiaquick PCR plates according to the manufacturer's instructions.

For *Pseudomonas aeruginosa*, plasmids from transformant colonies that received a dilution plating score of "2" or greater were isolated to obtain the genomic DNA insert responsible for growth inhibition as follows. *Pseudomonas aeruginosa* were grown in standard laboratory media (LB with carbenicillin at 100 μg/ml or Streptomycin 40 μg/ml to select for the plasmid). Growth was carried out at 30°C overnight in 100 ul culture wells in microtiter plates. To amplify insert DNA 2 ul of culture were placed into 25 ul Qiagen Hot Start PCR mix. PCR reactions were in 96 well microtiter plates. For plasmid pEP5S the following primers were used in the PCR reaction:

T7L1+: GTCGGCGATATAGGCGCCAGCAACCG (SEQ ID NO: 78590)

pStrA3: ATAATCGAGCATGAGTATCATACG (SEQ ID NO: 78591)

PCR was carried out in a PE GenAmp with the following cycle times:

Step 1. 95° C 15 min

Step 2. 94° C 45 sec

Step 3. 54° C 45 sec

Step 4. 72° C 1 minute

Step 5. Return to step 2, 29 times

Step 6. 72° C 10 minutes

Step 7. 4° C hold

The PCR products were cleaned using Qiagen Qiaquick PCR plates according to the manufacturer's instructions.

The purified PCR products were then directly cycle sequenced with Qiagen Hot Start PCR mix. The following primers were used in the sequencing reaction:

T7/L2: ATGCGTCCGGCGTAGAGGAT (SEQ ID NO: 78592)

PCR was carried out in a PE GenAmp with the following cycle times:

Step 1. 94° C 15 min

Step 2. 96° C 10 sec

Step 3. 50° C 5 sec

Step 4. 60 C 4 min

Step 5. Return to step 2, 24 times

Step 6. 4° C hold

The PCR products were cleaned using Qiagen Qiaquick PCR plates according to the manufacturer's instructions.

For *E. faecalis*, plasmids from transformant colonies that received a dilution plating score of "2" or greater were isolated to obtain the genomic DNA insert responsible for growth inhibition as follows. *E. faecalis* were grown in THB 10 μg/ml Erm at 30°C overnight in 100 ul culture wells

in microtiter plates. To amplify insert DNA 2 ul of culture were placed into 25 µl Qiagen Hot Start PCR mix. PCR reactions were in 96 well microtiter plates. The following primers were used in the PCR reaction:

pXylT5: CAGCAGTCTGAGTTATAAAATAG (SEQ ID NO: 78588) and the pEP/pAK1 primer.

PCR was carried out in a PE GenAmp with the following cycle times:

Step 1. 95° C 15 min

Step 2. 94° C 45 sec

Step 3. 54° C 45 sec

Step 4. 72° C 1 minute

Step 5. Return to step 2, 29 times

Step 6. 72° C 10 minutes

Step 7. 4° C hold

The PCR products were cleaned using Qiagen Qiaquick PCR plates according to the manufacturer's instructions.

The purified PCR products were then directly cycle sequenced with Qiagen Hot Start PCR mix. The following primers were used in the PCR reaction:

pXylT5: CAGCAGTCTGAGTTATAAAATAG (SEQ ID NO: 78588)

PCR was carried out in a PE GenAmp with the following cycle times:

Step 1. 94° C 15 min

Step 2. 96° C 10 sec

Step 3. 50° C 5 sec

Step 4. 60° C 4 min

Step 5. Return to step 2, 24 times

Step 6. 4° C hold

The PCR products were cleaned using Qiagen Qiaquick PCR plates according to the manufacturer's instructions.

The amplified genomic DNA inserts from each of the above procedures were subjected to automated sequencing. Sequence identification numbers (SEQ ID NOs) and clone names for the identified inserts are listed in Table IA and discussed below.

TABLE IA

SeqID	Clone Name	SeqID	Clone Name	SeqID	Clone Name	SeqID	Clone Name	SeqID	Clone Name
1	E3M10000001B01	1243	P33-1.C22	2485	E1M10000260G02	3727	P1M10000105C04	4969	S1M10000025G06
2	E3M10000001A02	1244	X3S107-17	2486	E1M10000260F04	3728	P1M10000105D04	4970	S1M10000025H06
3	E3M10000001B02	1245	P35-7	2487	E1M10000260A05	3729	P1M10000105C05	4971	S1M10000025H07
4	E3M10000001C02	1246	X3S118-9	2488	E1M10000260C05	3730	P1M10000105B06	4972	S1M10000025A08
5	E3M10000001D02	1247	X3S163-1	2489	E1M10000260E05	3731	P1M10000105C08	4973	S1M10000025D08
6	E3M10000001E02	1248	X3S204-7	2490	E1M10000260C07	3732	P1M10000105H08	4974	S1M10000025F08
7	E3M10000001F02	1249	X3S177-4	2491	E1M10000260G07	3733	P1M10000105D09	4975	S1M10000025H08
8	E3M10000001G02	1250	P342-3	2492	E1M10000260B08	3734	P1M10000110E01	4976	S1M10000025A09
9	E3M10000001H02	1251	SC21.1	2493	E1M10000260D08	3735	P1M10000110F01	4977	S1M10000025B09
10	E3M10000001E03	1252	SC17.1	2494	E1M10000260E08	3736	P1M10000110G01	4978	S1M10000025C09
11	E3M10000001G03	1253	SC13.1	2495	E1M10000260E09	3737	P1M10000110B02	4979	S1M10000025D09
12	E3M10000001H03	1254	MC9.6	2496	E1M10000260C10	3738	P1M10000110B03	4980	S1M10000025E09
13	E3M10000001D04	1255	Z60-P16	2497	E1M10000260D10	3739	P1M10000110F03	4981	S1M10000025F09
14	E3M10000001E04	1256	Z86-I21	2498	E1M10000260E10	3740	P1M10000110G03	4982	S1M10000025A10
15	E3M10000001F04	1257	E1M10000109A02	2499	E1M10000260G10	3741	P1M10000110D04	4983	S1M10000025C10
16	E3M10000001G04	1258	E1M10000109A11	2500	E1M10000260H10	3742	P1M10000110F04	4984	S1M10000025D10
17	E3M10000001H04	1259	E1M10000101F05	2501	E1M10000260H11	3743	P1M10000110B05	4985	S1M10000025F10
18	E3M10000001B05	1260	E1M10000101D06	2502	E1M10000260B12	3744	P1M10000110E05	4986	S1M10000025G10
19	E3M10000001D05	1261	E1M10000101A07	2503	E1M10000260D12	3745	P1M10000110B07	4987	S1M10000025H10
20	E3M10000001G05	1262	E1M10000101H07	2504	E1M10000260G12	3746	P1M10000110B08	4988	S1M10000025C11
21	E3M10000001A06	1263	E1M10000101H09	2505	E1M10000261F01	3747	P1M10000110F08	4989	S1M10000025E11
22	E3M10000001F06	1264	E1M10000101C12	2506	E1M10000261B02	3748	P1M10000110A09	4990	S1M10000025B12
23	E3M10000001B08	1265	E1M10000103B04	2507	E1M10000261H02	3749	P1M10000110E09	4991	S1M10000025F12
24	E3M10000001E08	1266	E1M10000103D11	2508	E1M10000261G04	3750	P1M10000110F09	4992	S1M10000026C01
25	E3M10000001C09	1267	E1M10000110G01	2509	E1M10000261H05	3751	P1M10000100F01	4993	S1M10000026E01
26	E3M10000001D09	1268	E1M10000110H01	2510	E1M10000261G06	3752	P1M10000098A02	4994	S1M10000026F01
27	E3M10000001E09	1269	E1M10000110E09	2511	E1M10000261H06	3753	P1M10000098B02	4995	S1M10000026G01
28	E3M10000001B10	1270	E1M10000110A12	2512	E1M10000261D08	3754	P1M10000098A03	4996	S1M10000026H01
29	E3M10000004D01	1271	E1M10000112F05	2513	E1M10000261F08	3755	P1M10000098D03	4997	S1M10000026A02
30	E3M10000004G01	1272	E1M10000113F02	2514	E1M10000261C09	3756	P1M10000098E04	4998	S1M10000026B02
31	E3M10000004D02	1273	E1M10000113A11	2515	E1M10000261H09	3757	P1M10000098G04	4999	S1M10000026H02
32	E3M10000004C03	1274	E1M10000111C03	2516	E1M10000261E10	3758	P1M10000098A05	5000	S1M10000026B03
33	E3M10000004A04	1275	E1M10000111E04	2517	E1M10000262E01	3759	P1M10000098C05	5001	S1M10000026F03

SeqID	Clone Name	SeqID	Clone Name	SeqID	Clone Name	SeqID	Clone Name	SeqID	Clone Name
34	E3M10000004F08	1276	E1M10000111F09	2518	E1M10000262C02	3760	P1M10000098G06	5002	S1M10000026G03
35	E3M10000004D10	1277	E1M10000115H01	2519	E1M10000262E02	3761	P1M10000098H06	5003	S1M10000026H03
36	E3M10000004F10	1278	E1M10000115G02	2520	E1M10000262F02	3762	P1M10000098C07	5004	S1M10000026A04
37	E3M10000004E11	1279	E1M10000115E03	2521	E1M10000262D03	3763	P1M10000098F07	5005	S1M10000026D04
38	E3M10000004H11	1280	E1M10000115G04	2522	E1M10000262G04	3764	P1M10000098A08	5006	S1M10000026F04
39	E3M10000005B01	1281	E1M10000115C06	2523	E1M10000262C05	3765	P1M10000098G08	5007	S1M10000026G04
40	E3M10000005C01	1282	E1M10000116B01	2524	E1M10000262A06	3766	P1M10000098H09	5008	S1M10000026H04
41	E3M10000005E01	1283	E1M10000106D02	2525	E1M10000262A07	3767	P1M10000098B11	5009	S1M10000026A05
42	E3M10000005E02	1284	E1M10000106G02	2526	E1M10000262E07	3768	P1M10000098C12	5010	S1M10000026B05
43	E3M10000005C03	1285	E1M10000106E04	2527	E1M10000262E08	3769	P1M10000099D01	5011	S1M10000026D05
44	E3M10000005D03	1286	E1M10000106F05	2528	E1M10000262B10	3770	P1M10000099G03	5012	S1M10000026F05
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46	E3M10000005C04	1288	E1M10000106H06	2530	E1M10000262G11	3772	P1M10000099A10	5014	S1M10000026H05
47	E3M10000005D04	1289	E1M10000106A08	2531	E1M10000262D12	3773	P1M10000099E10	5015	S1M10000026A06
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53	E3M10000005E08	1295	E1M10000123C09	2537	E1M10000263B07	3779	P1M10000106F04	5021	S1M10000026A07
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68	E3M10000007A02	1310	E1M10000118B05	2552	E1M10000264E04	3794	P1M10000108A03	5036	S1M10000026H09
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84	E3M10000008G09	1326	E1M10000132H04	2568	E1M10000265H05	3810	P1M10000109E11	5052	S1M10000026F12
85	E3M10000009D01	1327	E1M10000132G08	2569	E1M10000265C09	3811	P1M10000109B12	5053	S1M10000026G12
86	E3M10000009E02	1328	E1M10000133A06	2570	E1M10000265E09	3812	S4M10000001C01	5054	S1M10000027G01
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92	E3M10000009C09	1334	E1M10000144F03	2576	E1M10000266D02	3818	S4M10000008H10	5060	S1M10000027D03
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102	E3M10000011D03	1344	E1M10000124E02	2586	E1M10000267B05	3828	S4M10000010B05	5070	S1M10000027E05
103	E3M10000011C07	1345	E1M10000124G03	2587	E1M10000267A07	3829	S4M10000010D07	5071	S1M10000027F05
104	E3M10000011A09	1346	E1M10000124G04	2588	E1M10000267H07	3830	S4M10000010D08	5072	S1M10000027G05
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108	E3M10000012B02	1350	E1M10000125A02	2592	E1M10000267A10	3834	S4M10000010D10	5076	S1M10000027D06
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113	E3M10000012F07	1355	E1M10000120E05	2597	E1M10000267E12	3839	S4M10000011E10	5081	S1M10000027B07
114	E3M10000012G07	1356	E1M10000120A06	2598	E1M10000268F03	3840	S4M10000011F10	5082	S1M10000027D07
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124	E3M10000013A06	1366	E1M10000121G05	2608	E1M10000268E09	3850	S4M10000015E09	5092	S1M10000027G08
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126	E3M10000013D08	1368	E1M10000121E07	2610	E1M10000268G09	3852	S4M10000016A02	5094	S1M10000027B09
127	E3M10000013E08	1369	E1M10000121D08	2611	E1M10000268E10	3853	S4M10000020F08	5095	S1M10000027C09
128	E3M10000013D10	1370	E1M10000129G04	2612	E1M10000268A11	3854	S4M10000021E07	5096	S1M10000027D09
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131	E3M10000014B12	1373	E1M10000126E08	2615	E1M10000269D01	3857	S4M10000022B05	5099	S1M10000027G09
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139	E3M10000016G05	1381	E1M10000137B08	2623	E1M10000269A06	3865	S4M10000024G09	5107	S1M10000027G11
140	E3M10000016H05	1382	E1M10000137G09	2624	E1M10000269E07	3866	S4M10000024C11	5108	S1M10000027H11
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174	E3M10000022C05	1416	E1M10000152H08	2658	E1M10000272G09	3900	S4M10000036H11	5142	S1M10000028D07
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176	E3M10000022C06	1418	E1M10000153H03	2660	E1M10000273E01	3902	S4M10000037A08	5144	S1M10000028H07
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180	E3M10000022F08	1422	E1M10000153A09	2664	E1M10000273E05	3906	S4M10000033G05	5148	S1M10000028D08
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333	E3M10000029E08	1575	E1M10000193B07	2817	E1M10000277A08	4059	S1M10000005B04	5301	S1M10000031E12
334	E3M10000029G08	1576	E1M10000193C07	2818	E1M10000277C08	4060	S1M10000005D04	5302	S1M10000031F12
335	E3M10000029H08	1577	E1M10000193F07	2819	E1M10000277B10	4061	S1M10000005F04	5303	S1M10000032B01
336	E3M10000029C09	1578	E1M10000193C08	2820	E1M10000277G10	4062	S1M10000005C05	5304	S1M10000032C01
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338	E3M10000029F09	1580	E1M10000193B10	2822	E1M10000278G01	4064	S1M10000005E05	5306	S1M10000032H01
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356	E3M10000030G01	1598	E1M10000194B10	2840	E1M10000279C10	4082	S1M10000005B12	5324	S1M10000032A06
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361	E3M10000030G03	1603	E1M10000195G02	2845	E1M10000280B02	4087	S1M10000006F02	5329	S1M10000032B07
362	E3M10000030H03	1604	E1M10000195B03	2846	E1M10000280C03	4088	S1M10000006G02	5330	S1M10000032C07
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368	E3M10000030A05	1610	E1M10000195A08	2852	E1M10000280A07	4094	S1M10000006G03	5336	S1M10000032D08
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371	E3M10000030E05	1613	E1M10000195E10	2855	E1M10000280E08	4097	S1M10000006C04	5339	S1M10000032B09
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373	E3M10000030D06	1615	E1M10000195F11	2857	E1M10000280C09	4099	S1M10000006F04	5341	S1M10000032D09
374	E3M10000030F06	1616	E1M10000196B02	2858	E1M10000280H09	4100	S1M10000006G04	5342	S1M10000032E09
375	E3M10000030G06	1617	E1M10000196C02	2859	E1M10000280C10	4101	S1M10000006A05	5343	S1M10000032H09
376	E3M10000030H06	1618	E1M10000196E02	2860	E1M10000280C11	4102	S1M10000006D05	5344	S1M10000032A10
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391	E3M10000030D10	1633	E1M10000196D11	2875	E1M10000281F12	4117	S1M10000006B10	5359	S1M10000032F12
392	E3M10000030E10	1634	E1M10000196D12	2876	E1M10000282D01	4118	S1M10000006C10	5360	S1M10000032G12
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396	E3M10000030B11	1638	E1M10000197D04	2880	E1M10000282F03	4122	S1M10000006A12	5364	S1M10000033D02
397	E3M10000030H11	1639	E1M10000197B05	2881	E1M10000282C04	4123	S1M10000006B12	5365	S1M10000033F02
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409	E3M10000031E03	1651	E1M10000197B12	2893	E1M10000282G08	4135	S1M10000007G05	5377	S1M10000033A07
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464	E3M10000032F05	1706	E1M10000201H07	2948	E1M10000304C03	4190	S1M10000009G02	5432	S1M10000034C07
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468	E3M10000032C06	1710	E1M10000201H09	2952	E1M10000304G05	4194	S1M10000009F03	5436	S1M10000034G07
469	E3M10000032D06	1711	E1M10000201A10	2953	E1M10000304A06	4195	S1M10000009G03	5437	S1M10000034H07
470	E3M10000032G06	1712	E1M10000201G10	2954	E1M10000304F06	4196	S1M10000009H03	5438	S1M10000034A08
471	E3M10000032H06	1713	E1M10000201F12	2955	E1M10000304A08	4197	S1M10000009A04	5439	S1M10000034B08
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608	E3M10000035B08	1850	E1M10000230A08	3092	E1M10000289G06	4334	S1M10000013F02	5576	S1M10000037F05
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619	E3M10000035B10	1861	E1M10000231E03	3103	E1M10000290B01	4345	S1M10000013B05	5587	S1M10000037F07
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625	E3M10000035B11	1867	E1M10000231C09	3109	E1M10000290F05	4351	S1M10000013G06	5593	S1M10000037F08
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684	E3M10000036D10	1926	E1M10000216D12	3168	E1M10000295H04	4410	S1M10000014C06	5652	S1M10000038B09
685	E3M10000036F10	1927	E1M10000217D02	3169	E1M10000295A07	4411	S1M10000014D06	5653	S1M10000038D09
686	E3M10000036G10	1928	E1M10000217E02	3170	E1M10000295B07	4412	S1M10000014G06	5654	S1M10000038F09
687	E3M10000036H10	1929	E1M10000217H02	3171	E1M10000295C07	4413	S1M10000014H06	5655	S1M10000038H09
688	E3M10000036B11	1930	E1M10000217C04	3172	E1M10000295D08	4414	S1M10000014A07	5656	S1M10000038C10
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919	E3M10000041E05	2161	E1M10000239D01	3403	E1M10000314G03	4645	S1M10000018C10	5887	S1M10000043E07
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932	E3M10000041A08	2174	E1M10000239G11	3416	K1M10000019D06	4658	S1M10000018E12	5900	S1M10000043E10
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939	E3M10000041A09	2181	E1M10000240C08	3423	K1M10000032E11	4665	S1M10000019F01	5907	S1M10000043A12
940	E3M10000041B09	2182	E1M10000240F08	3424	K1M10000033E01	4666	S1M10000019A02	5908	S1M10000043B12
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943	E3M10000041F09	2185	E1M10000240H11	3427	K1M10000038D04	4669	S1M10000019A03	5911	S1M10000043E12
944	E3M10000041G09	2186	E1M10000240B12	3428	K1M10000039A12	4670	S1M10000019B03	5912	S1M10000044B01
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959	E3M10000041F11	2201	E1M10000241B11	3443	P1M10000021G03	4685	S1M10000019A07	5927	S1M10000044C06
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968	E3M10000042A02	2210	E1M10000243F03	3452	P1M10000026F04	4694	S1M10000019F08	5936	S1M10000044B08
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985	E3M10000042H08	2227	E1M10000244A04	3469	P1M10000033E03	4711	S1M10000019C12	5953	S1M10000044C11
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1004	E3M10000043A02	2246	E1M10000245B04	3488	P1M10000040E10	4730	S1M10000020B06	5972	S1M10000045E04
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1009	E3M10000043B03	2251	E1M10000245F06	3493	P1M10000042E08	4735	S1M10000020A07	5977	S1M10000045A06
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1014	E3M10000043G04	2256	E1M10000245C11	3498	P1M10000044F07	4740	S1M10000020A08	5982	S1M10000045C07
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1039	E3M10000043F10	2281	E1M10000247G01	3523	P1M10000055C08	4765	S1M10000021E01	6007	S1M10000045D12
1040	E3M10000043G10	2282	E1M10000247E02	3524	P1M10000055A11	4766	S1M10000021G01	6008	S1M10000045E12
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1044	E3M10000043G11	2286	E1M10000247B04	3528	P1M10000056F06	4770	S1M10000021E03	6012	S1M10000046D01
1045	E3M10000043H11	2287	E1M10000247H04	3529	P1M10000056C07	4771	S1M10000021G03	6013	S1M10000046E01
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1089	E3M10000050H09	2331	E1M10000250E04	3573	P1M10000067G05	4815	S1M10000022C02	6057	S1M10000046G10
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1091	E3M10000051C01	2333	E1M10000250A05	3575	P1M10000067C06	4817	S1M10000022B03	6059	S1M10000046A11
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1095	E3M10000051H03	2337	E1M10000250G09	3579	P1M10000068F04	4821	S1M10000022G03	6063	S1M10000046A12
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1097	E3M10000051B04	2339	E1M10000250E10	3581	P1M10000068F08	4823	S1M10000022C04	6065	S1M10000046C12
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1103	E3M10000051D06	2345	E1M10000251F04	3587	P1M10000070E03	4829	S1M10000022E05	6071	S1M10000047G01
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1109	E3M10000051A08	2351	E1M10000251H08	3593	P1M10000070B10	4835	S1M10000022H06	6077	S1M10000047G02
1110	E3M10000051B08	2352	E1M10000251H09	3594	P1M10000070G12	4836	S1M10000022B07	6078	S1M10000047A03
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1116	E3M10000051E09	2358	E1M10000251F12	3600	P1M10000073G03	4842	S1M10000022A08	6084	S1M10000047H03
1117	E3M10000051G09	2359	E1M10000252D01	3601	P1M10000073D04	4843	S1M10000022B08	6085	S1M10000047A04
1118	E3M10000051H09	2360	E1M10000252G02	3602	P1M10000073A06	4844	S1M10000022C08	6086	S1M10000047B04
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1121	E3M10000051D10	2363	E1M10000252B04	3605	P1M10000074B01	4847	S1M10000022G08	6089	S1M10000047E04
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1127	E3M10000051E11	2369	E1M10000252A07	3611	P1M10000075F02	4853	S1M10000022C11	6095	S1M10000047C05
1128	E3M10000051F11	2370	E1M10000252H07	3612	P1M10000075B03	4854	S1M10000022D11	6096	S1M10000047D05
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1133	E3M10000050B03	2375	E1M10000252E10	3617	P1M10000076D05	4859	S1M10000022G12	6101	S1M10000047A06
1134	E3M10000050C03	2376	E1M10000252E11	3618	P1M10000076C08	4860	S1M10000023B01	6102	S1M10000047B06
1135	E3M10000050D03	2377	E1M10000252E12	3619	P1M10000076D10	4861	S1M10000023D01	6103	S1M10000047C06
1136	E3M10000050E03	2378	E1M10000253A02	3620	P1M10000077E04	4862	S1M10000023E01	6104	S1M10000047E06
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1139	E3M10000050H08	2381	E1M10000253D04	3623	P1M10000077C08	4865	S1M10000023G02	6107	S1M10000047A07
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1144	E3M10000052G02	2386	E1M10000253A09	3628	P1M10000059B04	4870	S1M10000023D04	6112	S1M10000047H07
1145	E3M10000052B03	2387	E1M10000253D09	3629	P1M10000059H08	4871	S1M10000023E04	6113	S1M10000047A08
1146	E3M10000052E03	2388	E1M10000253E09	3630	P1M10000059H09	4872	S1M10000023F04	6114	S1M10000047B08
1147	E3M10000052G03	2389	E1M10000253F09	3631	P1M10000059B10	4873	S1M10000023A05	6115	S1M10000047C08
1148	E3M10000052B04	2390	E1M10000253G09	3632	P1M10000059B11	4874	S1M10000023D05	6116	S1M10000047E08
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1152	E3M10000052D05	2394	E1M10000253B11	3636	P1M10000060H04	4878	S1M10000023B07	6120	S1M10000047A09
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1155	E3M10000052G06	2397	E1M10000253G12	3639	P1M10000079A10	4881	S1M10000023F07	6123	S1M10000047D09
1156	E3M10000052H06	2398	E1M10000254A03	3640	P1M10000079B10	4882	S1M10000023G07	6124	S1M10000047E09
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1163	E3M10000052D12	2405	E1M10000254B06	3647	P1M10000080C06	4889	S1M10000023B09	6131	S1M10000047E10
1164	1008-H20	2406	E1M10000254A07	3648	P1M10000081G05	4890	S1M10000023D09	6132	S1M10000047F10
1165	1011-P20	2407	E1M10000254E07	3649	P1M10000081H05	4891	S1M10000023G09	6133	S1M10000047G10
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1167	1010-C11	2409	E1M10000254A08	3651	P1M10000081D12	4893	S1M10000023B10	6135	S1M10000047A11
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1170	1083-27	2412	E1M10000254A11	3654	P1M10000082A05	4896	S1M10000023E10	6138	S1M10000047E11
1171	1065-12	2413	E1M10000254C11	3655	P1M10000082C05	4897	S1M10000023F10	6139	S1M10000047F11
1172	221-41	2414	E1M10000254E12	3656	P1M10000082D05	4898	S1M10000023H10	6140	S1M10000047H11
1173	B17-6.O10	2415	E1M10000255C01	3657	P1M10000082E05	4899	S1M10000023A11	6141	S1M10000047A12
1174	910-B20	2416	E1M10000255G02	3658	P1M10000083B01	4900	S1M10000023B11	6142	S1M10000047B12
1175	B18-2.N21	2417	E1M10000255H02	3659	P1M10000083A11	4901	S1M10000023C11	6143	S1M10000047C12
1176	971-B20	2418	E1M10000255A04	3660	P1M10000083B12	4902	S1M10000023E11	6144	S1M10000047D12
1177	D1-1.A15	2419	E1M10000255D05	3661	P1M10000083C12	4903	S1M10000023F11	6145	S1M10000047E12
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1179	D1-2.B13	2421	E1M10000255G06	3663	P1M10000084A04	4905	S1M10000023A12	6147	S1M10000048C01
1180	D1-2.P21	2422	E1M10000255B08	3664	P1M10000084E04	4906	S1M10000023B12	6148	S1M10000048D01
1181	Z56-D2	2423	E1M10000255D09	3665	P1M10000084F08	4907	S1M10000023C12	6149	S1M10000048G01
1182	PJMF55	2424	E1M10000255F09	3666	P1M10000084E11	4908	S1M10000023D12	6150	S1M10000048H01
1183	R1-15.A13	2425	E1M10000255B10	3667	P1M10000085D06	4909	S1M10000023F12	6151	S1M10000048A02
1184	R1-19.H1	2426	E1M10000256F01	3668	P1M10000086B01	4910	S1M10000024D01	6152	S1M10000048B02
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1188	E1M10000007B04	2430	E1M10000256C05	3672	P1M10000086E05	4914	S1M10000024F02	6156	S1M10000048F02
1189	227-10	2431	E1M10000256E07	3673	P1M10000087E04	4915	S1M10000024H02	6157	S1M10000048G02
1190	709-F23	2432	E1M10000256E09	3674	P1M10000087F04	4916	S1M10000024D03	6158	S1M10000048H02
1191	801-C15	2433	E1M10000256A10	3675	P1M10000087C09	4917	S1M10000024E03	6159	S1M10000048A03
1192	801-H19	2434	E1M10000256F10	3676	P1M10000087F09	4918	S1M10000024F03	6160	S1M10000048B03
1193	804-P6	2435	E1M10000256C12	3677	P1M10000087A11	4919	S1M10000024A04	6161	S1M10000048C03
1194	807-D20	2436	E1M10000257C01	3678	P1M10000088C04	4920	S1M10000024C04	6162	S1M10000048E03
1195	B13-17.G8	2437	E1M10000257G01	3679	P1M10000088A07	4921	S1M10000024D04	6163	S1M10000048F03
1196	B5-6.C8	2438	E1M10000257A02	3680	P1M10000089G08	4922	S1M10000024H04	6164	S1M10000048G03
1197	B8-2.D9	2439	E1M10000257D02	3681	P1M10000089D11	4923	S1M10000024B05	6165	S1M10000048H03
1198	B15-8.P13	2440	E1M10000257H02	3682	P1M10000090E01	4924	S1M10000024E05	6166	S1M10000048E04
1199	T13-5.A2	2441	E1M10000257C03	3683	P1M10000090F06	4925	S1M10000024F05	6167	S1M10000048G04
1200	T12-3.I11	2442	E1M10000257F04	3684	P1M10000090F08	4926	S1M10000024G05	6168	S1M10000048H04
1201	T20-15.D4	2443	E1M10000257G04	3685	P1M10000090B11	4927	S1M10000024B06	6169	S1M10000048A05
1202	T24-15.G6	2444	E1M10000257B05	3686	P1M10000091A09	4928	S1M10000024E06	6170	S1M10000048B05
1203	T24-17.C6	2445	E1M10000257D05	3687	P1M10000091E09	4929	S1M10000024G06	6171	S1M10000048C05
1204	244.B12	2446	E1M10000257F06	3688	P1M10000091G10	4930	S1M10000024H06	6172	S1M10000048F05
1205	1042-J1	2447	E1M10000257G07	3689	P1M10000092B02	4931	S1M10000024A07	6173	S1M10000048G05
1206	195.F5	2448	E1M10000257H07	3690	P1M10000092E02	4932	S1M10000024C07	6174	S1M10000048H05
1207	25.D5	2449	E1M10000257H08	3691	P1M10000092B04	4933	S1M10000024E07	6175	S1M10000048A06
1208	25.D6	2450	E1M10000257A09	3692	P1M10000092F05	4934	S1M10000024G07	6176	S1M10000048B06
1209	177.F3	2451	E1M10000257D09	3693	P1M10000092F06	4935	S1M10000024H07	6177	S1M10000048C06
1210	525.H11	2452	E1M10000257G10	3694	P1M10000092D09	4936	S1M10000024A08	6178	S1M10000048E06
1211	632.N2	2453	E1M10000257H10	3695	P1M10000092B10	4937	S1M10000024B08	6179	S1M10000048A07
1212	633.B7	2454	E1M10000257A11	3696	P1M10000092B12	4938	S1M10000024E08	6180	S1M10000048C07
1213	671.I20	2455	E1M10000257C11	3697	P1M10000093A03	4939	S1M10000024F08	6181	S1M10000048E07
1214	676.B12	2456	E1M10000257F11	3698	P1M10000093B03	4940	S1M10000024G08	6182	S1M10000048F07
1215	643.B19	2457	E1M10000257B12	3699	P1M10000093F03	4941	S1M10000024H08	6183	S1M10000048G07
1216	720.O16	2458	E1M10000257F12	3700	P1M10000093H07	4942	S1M10000024B09	6184	S1M10000048H07
1217	666.H12	2459	E1M10000258C01	3701	P1M10000093C08	4943	S1M10000024B10	6185	S1M10000048B08
1218	98.D4	2460	E1M10000258H02	3702	P1M10000093B09	4944	S1M10000024D10	6186	S1M10000048C08
1219	844.B21	2461	E1M10000258G03	3703	P1M10000093E09	4945	S1M10000024F10	6187	S1M10000048D08
1220	P31-25-F3	2462	E1M10000258A04	3704	P1M10000094H03	4946	S1M10000024G10	6188	S1M10000048E08
1221	P335-8.H8	2463	E1M10000258C04	3705	P1M10000094F04	4947	S1M10000024A11	6189	S1M10000048F08

SeqID	Clone Name	SeqID	Clone Name	SeqID	Clone Name	SeqID	Clone Name	SeqID	Clone Name
1222	P347.2	2464	E1M10000258G04	3706	P1M10000094H04	4948	S1M10000024D11	6190	S1M10000048H08
1223	P31-11-J20	2465	E1M10000258C05	3707	P1M10000094A10	4949	S1M10000024G12	6191	S1M10000048A09
1224	P336-14.F20	2466	E1M10000258D05	3708	P1M10000095C01	4950	S1M10000025B01	6192	S1M10000048C09
1225	P31-27-M1	2467	E1M10000258F05	3709	P1M10000095E04	4951	S1M10000025C01	6193	S1M10000048D09
1226	P338-4.M21	2468	E1M10000258G05	3710	P1M10000095G04	4952	S1M10000025D01	6194	S1M10000048E09
1227	P334-8.L7	2469	E1M10000258A06	3711	P1M10000095C09	4953	S1M10000025E01	6195	S1M10000048F09
1228	P31-2-E16	2470	E1M10000258D06	3712	P1M10000102E05	4954	S1M10000025B02	6196	S1M10000048H09
1229	P335-3.J14	2471	E1M10000258B07	3713	P1M10000102B07	4955	S1M10000025A03	6197	S1M10000048A10
1230	P334-5.H2	2472	E1M10000258G07	3714	P1M10000103B05	4956	S1M10000025B03	6198	S1M10000048B10
1231	P31-33-N2	2473	E1M10000258G08	3715	P1M10000103D06	4957	S1M10000025C03	6199	S1M10000048C10
1232	P332-11.C20	2474	E1M10000258B09	3716	P1M10000103E08	4958	S1M10000025D03	6200	S1M10000048D10
1233	869.A23	2475	E1M10000258D09	3717	P1M10000104A02	4959	S1M10000025F03	6201	S1M10000048E10
1234	P317-2.A3	2476	E1M10000258F10	3718	P1M10000104H02	4960	S1M10000025D04	6202	S1M10000048G10
1235	P326-9.K2	2477	E1M10000258C11	3719	P1M10000104A03	4961	S1M10000025E04	6203	S1M10000048H10
1236	P323-8.P1	2478	E1M10000258F11	3720	P1M10000104E03	4962	S1M10000025G04	6204	S1M10000048A11
1237	P35-8	2479	E1M10000259C03	3721	P1M10000104F07	4963	S1M10000025B05	6205	S1M10000048C11
1238	P36-13.E2	2480	E1M10000259B04	3722	P1M10000104D11	4964	S1M10000025C05	6206	S1M10000048D11
1239	P38-1.G20	2481	E1M10000259E04	3723	P1M10000105D01	4965	S1M10000025F05	6207	S1M10000048F11
1240	P327-50.M10	2482	E1M10000259E05	3724	P1M10000105E02	4966	S1M10000025H05	6208	S1M10000048G11
1241	P328-8.D21	2483	E1M10000259B12	3725	P1M10000105C03	4967	S1M10000025B06	6209	S1M10000048H11
1242	P328-20.P20	2484	E1M10000260E02	3726	P1M10000105G03	4968	S1M10000025D06	6210	S1M10000048A12

EXAMPLE 3

Comparison Of Isolated Nucleic Acids to Known Sequences

The nucleotide sequences of the subcloned fragments from *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Salmonella typhimurium* obtained from the expression vectors discussed above were compared to known sequences from *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium* and other microorganisms as follows. First, to confirm that each clone originated from one location on the chromosome and was not chimeric, the nucleotide sequences of the selected clones were compared against the *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa* or *Salmonella typhimurium* genomic sequences to align the clone to the correct position on the chromosome. The NCBI BLASTN v 2.0.9 program was used for this comparison, and the incomplete *Staphylococcus aureus* genomic sequences licensed from TIGR, as well as the NCBI nonredundant GenBank database were used as the source of genomic data. *Salmonella typhimurium* sequences were compared to sequences available from the Genome Sequencing Center (http://genome.wustl.edu/gsc/salmonella.shtml), and the Sanger Centre (http://www.sanger.ac.uk/projects/S___typhi). *Pseudomonas aeruginosa* sequences were compared to a proprietary database and the NCBI GenBank database. The *E. faecalis* sequences were compared to a proprietary database.

The BLASTN analysis was performed using the default parameters except that the filtering was turned off. No further analysis was performed on inserts which resulted from the ligation of multiple fragments.

In general, antisense molecules and their complementary genes are identified as follows. First, all possible full length open reading frames (ORFs) are extracted from available genomic databases. Such databases include the GenBank nonredundant (nr) database, the unfinished genome database available from TIGR and the PathoSeq database developed by Incyte Genomics. The latter database comprises over 40 annotated bacterial genomes including complete ORF analysis. If databases are incomplete with regard to the bacterial genome of interest, it is not necessary to extract all ORFs in the genome but only to extract the ORFs within the portions of the available genomic sequences which are complementary to the clones of interest. Computer algorithms for identifying ORFs, such as GeneMark, are available and well known to those in the art. Comparison of the clone DNA to the complementary ORF(s) allows determination of whether the clone is a sense or antisense clone. Furthermore, each ORF extracted from the database can be compared to sequences in well annotated databases including the GenBank (nr) protein database, SWISSPROT and the like. A description of the gene or of a closely related gene in a closely related microorganism is often available in these databases. Similar methods are used to identify antisense clones corresponding to genes encoding non-translated RNAs.

In order to generate the gene identification data compiled in Table IB, each of the cloned nucleic acid sequences discussed above corresponding to SEQ ID NO.s 1-6213 was used to identify the corresponding *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa* or *Salmonella typhimurium* ORFs in the PathoSeq v.4.1 (March 2000 release) database of microbial genomic sequences. For this purpose, the NCBI BLASTN 2.0.9 computer algorithm was used. The default parameters were used except that filtering was turned off. The default parameters for the BLASTN and BLASTX analyses were:

Expectation value (e)=10

Alignment view options: pairwise
Filter query sequence (DUST with BLASTN, SEG with others)=T
Cost to open a gap (zero invokes behavior)=0
Cost to extend a gap (zero invokes behavior)=0
X dropoff value for gapped alignment (in bits) (zero invokes behavior)=0
Show GI's in deflines=F
Penalty for a nucleotide mismatch (BLASTN only)=!3
Reward for a nucleotide match (BLASTN only)=1
Number of one-line descriptions (V)=500
Number of alignments to show (B)=250
Threshold for extending hits=default
Perform gapped alignment (not available with BLASTX)=T
Query Genetic code to use=1
DB Genetic code (for TBLAST[nx] only=1
Number of processors to use=1
SeqAlign file
Believe the query defline=F
Matrix=BLOSUM62
Word Size= default
Effective length of the database (use zero for the real size)=0
Number of best hits from a region to keep=100
Length of region used to judge hits=20
Effective length of the search space (use zero for the real size)=0
Query strands to search against database (for BLAST[nx] and TBLASTX), 3 is both, 1 is top, 2 is bottom=3
Produce HTML output=F

Alternatively, ORFs were identified and refined by conducting a survey of the public and private data sources. Full-length gene protein and nucleotide sequences for these organisms were assembled from various sources. For *Pseudomonas aeruginosa*, gene sequences were adopted from the Pseudomonas genome sequencing project (downloaded from http://www.pseudomonas.com). For *Klebsiella pneumoniae, Staphylococcus aureus, Streptococcus pneumoniae* and *Salmonella typhi*, genomic sequences from PathoSeq v 4.1 (Mar 2000 release) was reanalyzed for ORFs using the gene finding software GeneMark v 2.4a, which was purchased from GenePro Inc. 451 Bishop St., N.W., Suite B, Atlanta, GA, 30318, USA.

Antisense clones were identified as those clones for which transcription from the inducible promoter would result in the expression of an RNA antisense to a complementary ORF, intergenic

or intragenic sequence. Those clones containing single inserts and that caused growth sensitivity upon induction are listed in Table IA.

The gene descriptions in the PathoSeq database derive from annotations available in the public sequence databases described above. Where a clone was found to share significant sequence identity to two or more adjacent ORFs, it was listed once for each ORF and the PathoSeq information for each ORF was compiled in Table IB.

Table IA lists the SEQ ID NOs. and clone names of the inserts which inhibited proliferation. This information was used to identify the ORFs (SEQ ID NOs.: 6214-42397) whose gene products (SEQ ID NOs. 42398-78581) were inhibited by the nucleic acids comprising the nucleotide sequences of SEQ ID NOs. 1-6213. Table IB lists the clone name and the PathoSeq Locus containing the clone.

TABLE IB

Clone Name	Gene LocusID	Clone Name	Gene LocusID	Clone Name	Gene LocusID
E3M10000001B01	EFA205257	E1M10000233C05	ECO103161	S1M10000005E05	SAU802496
E3M10000001B01	EFA205258	E1M10000233H05	ECO103224	S1M10000005C06	SAU802121
E3M10000001A02	EFA205257	E1M10000233H05	ECO103225	S1M10000005D06	SAU801183
E3M10000001A02	EFA205258	E1M10000233D08	ECO103185	S1M10000005D06	SAU801184
E3M10000001B02	EFA205225	E1M10000233F08	ECO103265	S1M10000005A07	SAU800967
E3M10000001B02	EFA201977	E1M10000233F08	ECO103266	S1M10000005B07	SAU802496
E3M10000001B02	EFA203137	E1M10000233A09	ECO104092	S1M10000005D07	SAU801264
E3M10000001C02	EFA200840	E1M10000233A09	ECO104093	S1M10000005A08	SAU802496
E3M10000001D02	EFA202003	E1M10000233E09	ECO103238	S1M10000005B08	SAU800548
E3M10000001E02	EFA200840	E1M10000233E09	ECO103239	S1M10000005D08	SAU800607
E3M10000001F02	EFA200807	E1M10000233F09	ECO103886	S1M10000005E08	SAU802496
E3M10000001G02	EFA205257	E1M10000233D10	ECO103242	S1M10000005B09	SAU800122
E3M10000001G02	EFA205258	E1M10000233D10	ECO103243	S1M10000005C09	SAU801481
E3M10000001H02	EFA200811	E1M10000233H10	ECO100094	S1M10000005D09	SAU800542
E3M10000001E03	EFA201987	E1M10000234E01	ECO103884	S1M10000005A10	SAU801723
E3M10000001E03	EFA205258	E1M10000234B02	ECO103886	S1M10000005A10	SAU801722
E3M10000001G03	EFA201987	E1M10000234G02	ECO103233	S1M10000005A11	SAU801644
E3M10000001G03	EFA205258	E1M10000234G02	ECO103234	S1M10000005C11	SAU801113
E3M10000001H03	EFA201987	E1M10000234C05	ECO103181	S1M10000005D11	SAU800547
E3M10000001H03	EFA205258	E1M10000234C07	ECO103844	S1M10000005E11	SAU800155
E3M10000001D04	EFA201980	E1M10000234C08	ECO103878	S1M10000005B12	SAU802160
E3M10000001D04	EFA201981	E1M10000234C08	ECO204942	S1M10000005B12	SAU603460
E3M10000001D04	EFA205229	E1M10000234F08	ECO103461	S1M10000005D12	SAU801644
E3M10000001E04	EFA201028	E1M10000234H08	ECO103226	S1M10000006F01	SAU801264
E3M10000001F04	EFA200811	E1M10000234F09	ECO103055	S1M10000006B02	SAU800381
E3M10000001G04	EFA201993	E1M10000234D10	ECO100876	S1M10000006E02	SAU802496
E3M10000001H04	EFA201980	E1M10000234G10	ECO100886	S1M10000006F02	SAU802160
E3M10000001H04	EFA201981	E1M10000234B12	ECO104010	S1M10000006G02	SAU802125
E3M10000001H04	EFA205229	E1M10000235D01	ECO102233	S1M10000006A03	SAU802496
E3M10000001B05	EFA201993	E1M10000235A03	ECO100798	S1M10000006B03	SAU802655
E3M10000001D05	EFA201974	E1M10000235H03	ECO103886	S1M10000006D03	SAU801740
E3M10000001D05	EFA201975	E1M10000235E04	ECO103236	S1M10000006E03	SAU801256
E3M10000001G05	EFA202001	E1M10000235B06	ECO103886	S1M10000006F03	SAU801434
E3M10000001G05	EFA202003	E1M10000235F06	ECO103481	S1M10000006G03	SAU801275
E3M10000001A06	EFA201028	E1M10000235B08	ECO103885	S1M10000006A04	SAU801139
E3M10000001F06	EFA201028	E1M10000235E08	ECO103161	S1M10000006B04	SAU802496
E3M10000001B08	EFA201028	E1M10000235B09	ECO101848	S1M10000006C04	SAU802158
E3M10000001E08	EFA200807	E1M10000235H09	ECO103481	S1M10000006E04	SAU801089
E3M10000001C09	EFA200839	E1M10000235H09	ECO103482	S1M10000006F04	SAU801644
E3M10000001D09	EFA201987	E1M10000235B10	ECO100886	S1M10000006G04	SAU801740
E3M10000001D09	EFA205258	E1M10000235A11	ECO102299	S1M10000006A05	SAU802224
E3M10000001E09	EFA201987	E1M10000235F12	ECO103233	S1M10000006A05	SAU802223
E3M10000001E09	EFA205258	E1M10000235F12	ECO103234	S1M10000006D05	SAU802496
E3M10000001B10	EFA205257	E1M10000236E01	ECO100095	S1M10000006G05	SAU801256
E3M10000001B10	EFA205258	E1M10000236A02	ECO102340	S1M10000006C06	SAU800331
E3M10000004D01	EFA201985	E1M10000236E02	ECO103878	S1M10000006C06	SAU800332
E3M10000004D01	EFA201984	E1M10000236E02	ECO204942	S1M10000006D06	SAU802496
E3M10000004D01	EFA202953	E1M10000236A03	ECO103287	S1M10000006F06	SAU800548
E3M10000004G01	EFA200839	E1M10000236D03	ECO102556	S1M10000006G06	SAU800006
E3M10000004D02	EFA202022	E1M10000236G03	ECO102655	S1M10000006A07	SAU800967
E3M10000004D02	EFA202028	E1M10000236A04	ECO103186	S1M10000006B07	SAU801760

Clone Name	Gene LocusID	Clone Name	Gene LocusID	Clone Name	Gene LocusID
E3M10000004D02	EFA202536	E1M10000236D04	ECO103481	S1M10000006C07	SAU800546
E3M10000004C03	EFA200412	E1M10000236G04	ECO103510	S1M10000006D07	SAU801105
E3M10000004A04	EFA201981	E1M10000236A05	ECO102847	S1M10000006E07	SAU802496
E3M10000004A04	EFA205229	E1M10000236F05	ECO103181	S1M10000006G07	SAU801731
E3M10000004F08	EFA201977	E1M10000236F05	ECO103182	S1M10000006A08	SAU802496
E3M10000004F08	EFA203137	E1M10000236H06	ECO103242	S1M10000006E08	SAU802238
E3M10000004D10	EFA201999	E1M10000236H06	ECO103243	S1M10000006A10	SAU802496
E3M10000004D10	EFA201997	E1M10000236D08	ECO103669	S1M10000006B10	SAU802240
E3M10000004F10	EFA200624	E1M10000236F09	ECO103228	S1M10000006C10	SAU802496
E3M10000004E11	EFA200624	E1M10000236C10	ECO102227	S1M10000006G10	SAU802247
E3M10000004H11	EFA205225	E1M10000236A11	ECO102986	S1M10000006G10	SAU802248
E3M10000004H11	EFA201977	E1M10000236C11	ECO101088	S1M10000006B11	SAU801618
E3M10000004H11	EFA203137	E1M10000236F12	ECO101355	S1M10000006G11	SAU802119
E3M10000005B01	EFA201984	E1M10000237A02	ECO103161	S1M10000006G11	SAU802118
E3M10000005B01	EFA201983	E1M10000237B02	ECO101830	S1M10000006A12	SAU800548
E3M10000005C01	EFA200839	E1M10000237E04	ECO103217	S1M10000006B12	SAU802558
E3M10000005E01	EFA201977	E1M10000237E04	ECO103218	S1M10000007F01	SAU801256
E3M10000005E01	EFA203137	E1M10000237H04	ECO103624	S1M10000007B02	SAU800591
E3M10000005E02	EFA201977	E1M10000237H04	ECO103625	S1M10000007B02	SAU800592
E3M10000005E02	EFA203137	E1M10000237G06	ECO103232	S1M10000007F02	SAU801366
E3M10000005C03	EFA200811	E1M10000237G06	ECO103233	S1M10000007G02	SAU801138
E3M10000005C03	EFA200812	E1M10000237C07	ECO103886	S1M10000007A03	SAU801899
E3M10000005D03	EFA200811	E1M10000237G07	ECO103263	S1M10000007D03	SAU802496
E3M10000005D03	EFA200812	E1M10000237H07	ECO102267	S1M10000007G03	SAU800967
E3M10000005E03	EFA200811	E1M10000237A08	ECO103217	S1M10000007C04	SAU801740
E3M10000005E03	EFA200812	E1M10000237A08	ECO103216	S1M10000007E04	SAU802496
E3M10000005C04	EFA200660	E1M10000237B08	ECO101185	S1M10000007F04	SAU800478
E3M10000005C04	EFA200661	E1M10000237B08	ECO101186	S1M10000007C05	SAU800547
E3M10000005D04	EFA200839	E1M10000237D08	ECO103217	S1M10000007G05	SAU800548
E3M10000005H04	EFA200839	E1M10000237D08	ECO103216	S1M10000007C06	SAU801900
E3M10000005G05	EFA201977	E1M10000237E08	ECO103262	S1M10000007D06	SAU800547
E3M10000005G05	EFA203137	E1M10000237E08	ECO103878	S1M10000007E06	SAU801113
E3M10000005A07	EFA200811	E1M10000237E08	ECO204942	S1M10000007C07	SAU801904
E3M10000005A07	EFA200812	E1M10000237B09	ECO101844	S1M10000007E07	SAU801618
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E3M10000052G03	EFA200326	E1M10000291G05	ECO102555	S1M10000029F10	SAU800266
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1010-C11	ECO101324	E1M10000293G02	ECO103886	S1M10000030G03	SAU800542
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B17-6.O10	ECO103884	E1M10000293G05	ECO103243	S1M10000030D05	SAU800759
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807-D20	ECO100366	E1M10000295B07	ECO100179	S1M10000030G10	SAU800019
807-D20	ECO100367	E1M10000295B07	ECO100180	S1M10000030H10	SAU802654
B13-17.G8	ECO101111	E1M10000295C07	ECO103224	S1M10000030A11	SAU800517
B5-6.C8	ECO101475	E1M10000295C07	ECO103225	S1M10000030A11	SAU202623
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B15-8.P13	ECO101328	E1M10000295F08	ECO103160	S1M10000030G11	SAU800811
B15-8.P13	ECO101329	E1M10000295G08	ECO103217	S1M10000030C12	SAU801647
T13-5.A2	ECO103059	E1M10000295G08	ECO103218	S1M10000030C12	SAU801646
T12-3.I11	ECO102857	E1M10000295B09	ECO103236	S1M10000030E12	SAU800537
T20-15.D4	ECO101475	E1M10000295F09	ECO103881	S1M10000030G12	SAU801526
T20-15.D4	ECO101476	E1M10000295F09	ECO103882	S1M10000031B01	SAU802240
T20-15.D4	ECO201962	E1M10000295G09	ECO103263	S1M10000031H01	SAU800023
T24-15.G6	ECO103059	E1M10000295D10	ECO103101	S1M10000031B02	SAU802247
T24-17.C6	ECO102857	E1M10000295H10	ECO103263	S1M10000031E02	SAU801912
244.B12	ECO101763	E1M10000295B11	ECO103229	S1M10000031F02	SAU802231
244.B12	ECO101764	E1M10000295F11	ECO100954	S1M10000031F02	SAU802230
244.B12	ECO101765	E1M10000295G12	ECO103494	S1M10000031G02	SAU802235
1042-J1	ECO100702	E1M10000312D11	ECO104091	S1M10000031G02	SAU802234
1042-J1	ECO100703	E1M10000312D11	ECO104092	S1M10000031H02	SAU801355
195.F5	ECO102842	E1M10000296B01	ECO102304	S1M10000031A03	SAU802250
25.D5	ECO103059	E1M10000296C02	ECO102466	S1M10000031E03	SAU801134
25.D6	ECO103059	E1M10000296C02	ECO102467	S1M10000031E03	SAU801135
177.F3	ECO102309	E1M10000296D02	ECO103235	S1M10000031F03	SAU802240
525.H11	ECO102857	E1M10000296D02	ECO103236	S1M10000031G03	SAU801505
632.N2	ECO104277	E1M10000296D02	ECO103237	S1M10000031A04	SAU801434
633.B7	ECO103479	E1M10000296H02	ECO102556	S1M10000031A04	SAU302892
671.I20	ECO103478	E1M10000296C03	ECO100150	S1M10000031B04	SAU800543
676.B12	ECO103479	E1M10000296C03	ECO100151	S1M10000031C04	SAU800738
643.B19	ECO100702	E1M10000296E03	ECO101086	S1M10000031C04	SAU800737
720.O16	ECO103884	E1M10000296H03	ECO103227	S1M10000031E04	SAU800542
666.H12	ECO103478	E1M10000296H03	ECO103228	S1M10000031F04	SAU801517
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98.D4	ECO103263	E1M10000296G04	ECO102144	S1M10000031G04	SAU302611
844.B21	ECO102144	E1M10000296F05	ECO103886	S1M10000031G04	SAU302882
P31-25-F3	ECO101686	E1M10000296G05	ECO101467	S1M10000031F05	SAU800548
P335-8.H8	ECO101041	E1M10000296H05	ECO103094	S1M10000031D06	SAU801526
P347.2	ECO101086	E1M10000296A06	ECO100194	S1M10000031G06	SAU800548
P31-11-J20	ECO103228	E1M10000296A06	ECO100195	S1M10000031H06	SAU600582
P336-14.F20	ECO101370	E1M10000296G07	ECO102827	S1M10000031C07	SAU801760
P31-27-M1	ECO103423	E1M10000296G07	ECO102828	S1M10000031D07	SAU801181
P338-4.M21	ECO100139	E1M10000296H07	ECO103220	S1M10000031E07	SAU800016
P334-8.L7	ECO101256	E1M10000296H07	ECO103221	S1M10000031A08	SAU802365
P31-2-E16	ECO101686	E1M10000296E08	ECO100886	S1M10000031D08	SAU801790
P335-3.J14	ECO100523	E1M10000296F08	ECO103218	S1M10000031E08	SAU800547
P334-5.H2	ECO100139	E1M10000296G08	ECO103734	S1M10000031F08	SAU801264
P31-33-N2	ECO103241	E1M10000296H08	ECO100809	S1M10000031C09	SAU801193
P332-11.C20	ECO102827	E1M10000296H08	ECO100810	S1M10000031D09	SAU800019
P332-11.C20	ECO102828	E1M10000296A09	ECO100194	S1M10000031G09	SAU800006
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P323-8.P1	ECO101685	E1M10000296G12	ECO100095	S1M10000031F10	SAU800244
P35-8	ECO103692	E1M10000298C01	ECO101438	S1M10000031G10	SAU800962
P36-13.E2	ECO103059	E1M10000298G01	ECO104148	S1M10000031A11	SAU801741
P38-1.G20	ECO102227	E1M10000298G01	ECO104149	S1M10000031B11	SAU801908
P327-50.M10	ECO103242	E1M10000298G02	ECO102636	S1M10000031C11	SAU802152
P327-50.M10	ECO103243	E1M10000298C03	ECO103238	S1M10000031F11	SAU800312
P328-8.D21	ECO103240	E1M10000298C03	ECO103239	S1M10000031G11	SAU801234
P328-8.D21	ECO103241	E1M10000298D03	ECO103886	S1M10000031H11	SAU800962
P328-20.P20	ECO100541	E1M10000298H03	ECO103262	S1M10000031B12	SAU801621
P33-1.C22	ECO103227	E1M10000298H03	ECO103878	S1M10000031C12	SAU801741
X3S107-17	ECO101475	E1M10000298H03	ECO204942	S1M10000031E12	SAU801275
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X3S107-17	ECO201962	E1M10000298E04	ECO100431	S1M10000032B01	SAU802654
P35-7	ECO103928	E1M10000298H04	ECO100809	S1M10000032C01	SAU800548
X3S118-9	ECO103263	E1M10000298H04	ECO100808	S1M10000032F01	SAU800525
X3S163-1	ECO103423	E1M10000298C05	ECO103234	S1M10000032F01	SAU800524
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X3S177-4	ECO101161	E1M10000298C05	ECO103236	S1M10000032H01	SAU802111
P342-3	ECO102104	E1M10000298D05	ECO101539	S1M10000032E02	SAU801096
SC21.1	ECO103224	E1M10000298D05	ECO101540	S1M10000032G02	SAU800830
SC17.1	ECO102087	E1M10000298C06	ECO101844	S1M10000032G02	SAU800829
SC13.1	ECO101347	E1M10000298D06	ECO103886	S1M10000032A03	SAU802686
SC13.1	ECO101348	E1M10000298G06	ECO100096	S1M10000032C03	SAU800771
MC9.6	ECO102929	E1M10000298B07	ECO100095	S1M10000032D03	SAU801235
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Z60-P16	ECO103243	E1M10000298G07	ECO103233	S1M10000032G03	SAU801269
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E1M10000111C03	ECO103238	E1M10000311C07	ECO103263	S1M10000032A08	SAU800217
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E1M10000220B03	ECO101324	S1M10000002D08	SAU801900	S1M10000047G05	SAU801669
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E1M10000222F05	ECO101476	S1M10000003C06	SAU800014	S1M10000047A10	SAU801301
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E1M10000225F04	ECO101583	S1M10000003B12	SAU302892	S1M10000048C01	SAU800753
E1M10000225A06	ECO103218	S1M10000003C12	SAU800548	S1M10000048D01	SAU802654
E1M10000225B06	ECO101259	S1M10000003F12	SAU801621	S1M10000048G01	SAU800363
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E1M10000225H09	ECO101989	S1M10000004G01	SAU802496	S1M10000048D02	SAU802548
E1M10000225F10	ECO101684	S1M10000004C02	SAU802496	S1M10000048D02	SAU104011
E1M10000225D12	ECO102966	S1M10000004F02	SAU800546	S1M10000048E02	SAU800753
E1M10000225D12	ECO102967	S1M10000004B03	SAU800257	S1M10000048F02	SAU802107
E1M10000225G12	ECO101128	S1M10000004B03	SAU800258	S1M10000048G02	SAU800019
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E1M10000226B02	ECO103515	S1M10000004A04	SAU802655	S1M10000048B03	SAU801184
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E1M10000226F02	ECO102999	S1M10000004D04	SAU802223	S1M10000048E03	SAU802586
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E1M10000226H06	ECO103848	S1M10000004D06	SAU800006	S1M10000048E04	SAU801183
E1M10000226A08	ECO104132	S1M10000004E06	SAU802240	S1M10000048G04	SAU802247
E1M10000226D08	ECO101753	S1M10000004F06	SAU800152	S1M10000048H04	SAU802586
E1M10000226D09	ECO100430	S1M10000004A07	SAU802503	S1M10000048H04	SAU802585
E1M10000226D09	ECO100431	S1M10000004D07	SAU802496	S1M10000048A05	SAU801263
E1M10000226B10	ECO102113	S1M10000004E07	SAU802177	S1M10000048B05	SAU800753
E1M10000226D10	ECO101623	S1M10000004E07	SAU802176	S1M10000048C05	SAU801891
E1M10000226E10	ECO102714	S1M10000004F07	SAU801683	S1M10000048F05	SAU801184
E1M10000226G11	ECO103244	S1M10000004G07	SAU801644	S1M10000048G05	SAU800542
E1M10000226B12	ECO101916	S1M10000004G07	SAU801643	S1M10000048H05	SAU800546
E1M10000226F12	ECO100240	S1M10000004B08	SAU801346	S1M10000048A06	SAU800546
E1M10000227E03	ECO100975	S1M10000004B08	SAU200535	S1M10000048B06	SAU801184
E1M10000227E03	ECO201249	S1M10000004C08	SAU802503	S1M10000048C06	SAU801670
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E1M10000227G03	ECO101459	S1M10000004D08	SAU202623	S1M10000048E06	SAU801186
E1M10000227E04	ECO104148	S1M10000004F08	SAU802224	S1M10000048A07	SAU801253
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E1M10000227C05	ECO104165	S1M10000004C09	SAU802496	S1M10000048G07	SAU800520
E1M10000227C07	ECO101423	S1M10000004F09	SAU802496	S1M10000048G07	SAU800519
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E1M10000227D08	ECO103911	S1M10000004D10	SAU801618	S1M10000048D08	SAU300619
E1M10000227B09	ECO102736	S1M10000004A11	SAU801475	S1M10000048E08	SAU802224
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E1M10000227E11	ECO103723	S1M10000004A12	SAU801208	S1M10000048A09	SAU800547
E1M10000227E11	ECO103724	S1M10000004C12	SAU800519	S1M10000048C09	SAU800548
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E1M10000227D12	ECO104144	S1M10000004E12	SAU800528	S1M10000048F09	SAU802238
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E1M10000232B03	ECO101324	S1M10000005C01	SAU802496	S1M10000048C10	SAU800367
E1M10000232H03	ECO103097	S1M10000005E01	SAU800996	S1M10000048D10	SAU802590
E1M10000232C07	ECO100170	S1M10000005B02	SAU802243	S1M10000048E10	SAU802590
E1M10000232F07	ECO103797	S1M10000005D02	SAU800519	S1M10000048G10	SAU802238
E1M10000232F07	ECO103798	S1M10000005E02	SAU802655	S1M10000048H10	SAU802240
E1M10000232G07	ECO104010	S1M10000005F02	SAU801644	S1M10000048A11	SAU802224
E1M10000232A08	ECO100850	S1M10000005F02	SAU801643	S1M10000048C11	SAU802217
E1M10000232G08	ECO100875	S1M10000005A03	SAU802310	S1M10000048D11	SAU802090
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E1M10000233C01	ECO103886	S1M10000005F03	SAU802262	S1M10000048G11	SAU801186
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E1M10000233H03	ECO103239	S1M10000005F04	SAU800362	S1M10000048D12	SAU800249
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E1M10000233A05	ECO102553	S1M10000005D05	SAU801644		

Table IC provides a cross reference between PathoSeq Gene Loci listed in Table IB and the SEQ ID NOs. of the corresponding PathoSeq polypeptides and the SEQ ID NOs. of the nucleic acids which encode them. The Gene Locus IDs provided in Table IC each comprise a nine digit alpha-numeric identifier that can be used to determine the organism from which each Gene Locus and corresponding SEQ ID NOs. were identified. Specifically, the first letter of the Gene Locus ID corresponds to the first letter of the genus name of the organism described herein from which the Gene Locus was identified and the second and third letters of the Gene Locus ID correspond to the first two letters of the species name of this organism. For example, the identifier EFA205257 describes a gene locus identified from *Enterococcus faecalis*. In those instances where the three letter identifier is the same for different organisms, the exact identity of the organism which corresponds to the Gene Locus ID can be determined by referring to the organism designation in the sequence listing for the coding nucleic acid or polypeptide SEQ ID NO. that corresponds to the particular Gene Locus ID.

TABLE IC

DNA SeqID	Protein SeqID	Gene LocusID	DNA SeqID	Protein SeqID	Gene LocusID	DNA SeqID	Protein SeqID	Gene LocusID
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6215	42399	EFA205258	18277	54461	CJU100848	30338	66522	PAE203654
6216	42400	EFA205225	18278	54462	CJU100855	30339	66523	PAE203656
6217	42401	EFA201977	18279	54463	CJU100856	30340	66524	PAE203658
6218	42402	EFA203137	18280	54464	CJU100859	30341	66525	PAE203668
6219	42403	EFA200840	18281	54465	CJU100860	30342	66526	PAE203670
6220	42404	EFA202003	18282	54466	CJU100861	30343	66527	PAE203672
6221	42405	EFA200807	18283	54467	CJU100862	30344	66528	PAE203677
6222	42406	EFA200811	18284	54468	CJU100863	30345	66529	PAE203684
6223	42407	EFA201987	18285	54469	CJU100866	30346	66530	PAE203691
6224	42408	EFA201980	18286	54470	CJU100870	30347	66531	PAE203698
6225	42409	EFA201981	18287	54471	CJU100871	30348	66532	PAE203722
6226	42410	EFA205229	18288	54472	CJU100872	30349	66533	PAE203732
6227	42411	EFA201028	18289	54473	CJU100885	30350	66534	PAE203735
6228	42412	EFA201993	18290	54474	CJU100886	30351	66535	PAE203739
6229	42413	EFA201974	18291	54475	CJU100888	30352	66536	PAE203740
6230	42414	EFA201975	18292	54476	CJU100890	30353	66537	PAE203741
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6232	42416	EFA200839	18294	54478	CJU100896	30355	66539	PAE203743
6233	42417	EFA201985	18295	54479	CJU100903	30356	66540	PAE203744
6234	42418	EFA201984	18296	54480	CJU100923	30357	66541	PAE203751
6235	42419	EFA202953	18297	54481	CJU100925	30358	66542	PAE203754
6236	42420	EFA202022	18298	54482	CJU100929	30359	66543	PAE203755
6237	42421	EFA202028	18299	54483	CJU100938	30360	66544	PAE203757
6238	42422	EFA202536	18300	54484	CJU100944	30361	66545	PAE203758
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6240	42424	EFA201999	18302	54486	CJU100955	30363	66547	PAE203766
6241	42425	EFA201997	18303	54487	CJU100961	30364	66548	PAE203774
6242	42426	EFA200624	18304	54488	CJU100965	30365	66549	PAE203796
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6245	42429	EFA200660	18307	54491	CJU100970	30368	66552	PAE203800
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8562	44746	ABA101163	20624	56808	ECO104239	32685	68869	PRT102997
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11241	47425	BCE102018	23303	59487	KPN301406	35364	71548	SHA100979
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12374	48558	BFR103716	24436	60620	LMO101222	36497	72681	SPA100379
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15323	51507	CAC100165	27385	63569	MGE100333	39446	75630	STY101426
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15328	51512	CAC100193	27390	63574	MGE100346	39451	75635	STY101451
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15403	51587	CAC100626	27465	63649	MLP100072	39526	75710	STY101789
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15436	51620	CAC100852	27498	63682	MLP100182	39559	75743	STY101844
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15473	51657	CAC101038	27535	63719	MLP100341	39596	75780	STY102007
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15512	51696	CAC101231	27574	63758	MLP100499	39635	75819	STY102227
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15527	51711	CAC101338	27589	63773	MLP100525	39650	75834	STY102310
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15533	51717	CAC101393	27595	63779	MLP100543	39656	75840	STY102330
15534	51718	CAC101396	27596	63780	MLP100560	39657	75841	STY102331
15535	51719	CAC101411	27597	63781	MLP100561	39658	75842	STY102345
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15770	51954	CAC102601	27832	64016	MLP101379	39893	76077	STY103470
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15824	52008	CAC102804	27886	64070	MPN100010	39947	76131	STY103809
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15826	52010	CAC102817	27888	64072	MPN100032	39949	76133	STY103813
15827	52011	CAC102832	27889	64073	MPN100037	39950	76134	STY103815
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15831	52015	CAC102864	27893	64077	MPN100049	39954	76138	STY103825
15832	52016	CAC102868	27894	64078	MPN100067	39955	76139	STY103826
15833	52017	CAC102879	27895	64079	MPN100073	39956	76140	STY103840
15834	52018	CAC102880	27896	64080	MPN100074	39957	76141	STY103841
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15840	52024	CAC102908	27902	64086	MPN100083	39963	76147	STY103853
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15847	52031	CAC102940	27909	64093	MPN100094	39970	76154	STY103871
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15897	52081	CAC103209	27959	64143	MPN100223	40020	76204	STY104029
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16006	52190	CBO100136	28068	64252	MPN100538	40129	76313	STY104568
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16009	52193	CBO100146	28071	64255	MPN100557	40132	76316	STY104576
16010	52194	CBO100154	28072	64256	MPN100558	40133	76317	STY104578
16011	52195	CBO100159	28073	64257	MPN100560	40134	76318	STY104579
16012	52196	CBO100164	28074	64258	MPN100564	40135	76319	STY104582
16013	52197	CBO100172	28075	64259	MPN100566	40136	76320	STY104584
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16016	52200	CBO100202	28078	64262	MPN100578	40139	76323	STY104593
16017	52201	CBO100209	28079	64263	MPN100579	40140	76324	STY104599
16018	52202	CBO100210	28080	64264	MPN100580	40141	76325	STY104601
16019	52203	CBO100211	28081	64265	MPN100582	40142	76326	STY104615
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16031	52215	CBO100253	28093	64277	MPN100606	40154	76338	STY104879
16032	52216	CBO100256	28094	64278	MPN100608	40155	76339	STY104903
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16052	52236	CBO100362	28114	64298	MPN100644	40175	76359	STY107465
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16060	52244	CBO100413	28122	64306	MPN100653	40183	76367	TPA100024
16061	52245	CBO100415	28123	64307	MPN100654	40184	76368	TPA100028
16062	52246	CBO100417	28124	64308	MPN100655	40185	76369	TPA100029
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16066	52250	CBO100441	28128	64312	MPN100659	40189	76373	TPA100051
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16068	52252	CBO100452	28130	64314	MPN100661	40191	76375	TPA100055
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16070	52254	CBO100465	28132	64316	MPN100663	40193	76377	TPA100057
16071	52255	CBO100467	28133	64317	MPN100664	40194	76378	TPA100059
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16073	52257	CBO100481	28135	64319	MPN100666	40196	76380	TPA100061
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16075	52259	CBO100497	28137	64321	MPN100672	40198	76382	TPA100066
16076	52260	CBO100509	28138	64322	MPN100673	40199	76383	TPA100070
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16555	52739	CBO103360	28617	64801	MTU202871	40678	76862	UUR100475
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16615	52799	CBO103696	28677	64861	MTU203266	40738	76922	UUR100593
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17583	53767	CDP100387	29645	65829	NME200871	41706	77890	YPS000872
17584	53768	CDP100388	29646	65830	NME200872	41707	77891	YPS000874
17585	53769	CDP100396	29647	65831	NME200873	41708	77892	YPS000890
17586	53770	CDP100399	29648	65832	NME200879	41709	77893	YPS000894
17587	53771	CDP100400	29649	65833	NME200881	41710	77894	YPS000900
17588	53772	CDP100404	29650	65834	NME200882	41711	77895	YPS000901
17589	53773	CDP100408	29651	65835	NME200887	41712	77896	YPS000907
17590	53774	CDP100409	29652	65836	NME200892	41713	77897	YPS000909
17591	53775	CDP100410	29653	65837	NME200893	41714	77898	YPS000920
17592	53776	CDP100414	29654	65838	NME200897	41715	77899	YPS000925
17593	53777	CDP100417	29655	65839	NME200899	41716	77900	YPS000930
17594	53778	CDP100418	29656	65840	NME200901	41717	77901	YPS000931
17595	53779	CDP100421	29657	65841	NME200903	41718	77902	YPS000933